

# Emergencies in Neurology

Volume II

Mamta Bhushan Singh  
Rohit Bhatia  
*Editors*

*Second Edition*



Springer

---

# Emergencies in Neurology

---

Mamta Bhushan Singh • Rohit Bhatia  
Editors

# Emergencies in Neurology

Volume II

Second Edition

 Springer



*Editors*

Mamta Bhushan Singh  
Department of Neurology  
All India Institute of Medical Sciences  
New Delhi  
India

Rohit Bhatia  
Department of Neurology  
All India Institute of Medical Sciences  
New Delhi  
India

ISBN 978-981-13-7379-4                      ISBN 978-981-13-7381-7 (eBook)

<https://doi.org/10.1007/978-981-13-7381-7>

© Byword Books Private Limited 2011 First Edition

© The Editor(s) (if applicable) and The Author(s) 2019 Second Edition

This work is subject to copyright. All rights are reserved by the Publishers, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publishers, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publishers nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publishers remain neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Co-publishing partnership between Bywords Books Private Limited and Springer Nature India Private Limited

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.

The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

---

## Preface to the Second Edition

The first edition of *Emergencies in Neurology* came in 2011. We acknowledge the appreciation of many readers, especially younger colleagues and residents, who found the book useful. This encouragement from readers, some inadvertent errors that had crept into the first edition and needed correction and the intervening years where research has led to further progress and availability of new evidence leading to refinement of some treatments, made us consider working on a second edition.

The basic format of the second edition remains the same as that of the first. Each chapter includes a discussion outlining a systematic approach to a neurological emergency. This is followed by a comprehensive description of the best management recommended for that emergency. In the second edition, an attempt has been made to update management keeping in mind the latest evidence that is currently available. Substantive changes have been made in several chapters and minor improvements in others.

The second edition is in two volumes. This has been done to accommodate five new chapters and one extra chapter created as a previous one became too large and had to be divided into two. The extra new chapters cover important subjects that we were not able to include in the first edition. Distinguished authors have contributed to each of these. We hope that the newly added chapters broaden the scope of this edition and increase its value for the readers.

Neurological disorders may be visualized as forming a wide spectrum with chronic illnesses at one end and acute emergencies at the other. Chronic neurological disorders have a relatively protracted temporal profile during which they provide ample opportunity for not just clinical evaluation and anatomical localization but also for performing numerous investigations at a relatively convenient pace. On the other hand, neurological emergencies are very different in that they appear abruptly, generally have a stormy course and necessitate a rushed and yet balanced approach.

While many voluminous and scholarly textbooks of neurology are available to readers worldwide, having a small, sharp, evidence-based and updated account of how to approach critically ill patients seemed like a good idea to us. Emergency management can be a challenge as well as can reap rich dividends if it is understood and practised with maturity, skill and energy. The nihilism associated with neurological emergencies in the past is increasingly being replaced by aggressive emergency management leading to better outcomes. Additionally, in resource-crunched areas of the globe, it may not always be a neurologist who attends to patients

presenting with neurological emergencies. Therefore, it seems logical to have a handbook that is comprehensive and yet not overwhelming in detail.

This book has been conceived and written keeping in mind the needs felt by a first contact doctor who may be a neurology trainee, a seasoned or junior neurology consultant, a physician or an intern. Special attention has been focused on the various aspects of management of patients in the emergency department from the point of taking a good clinical history, performing a quick and targeted clinical examination to investigating and starting treatment. The relevant differential diagnoses that should be thought of in various circumstances and how they can be excluded have been dealt with in sufficient detail. A carefully selected list of citations at the end of each chapter will be useful for the reader seeking more advanced and detailed information.

In recognizing and expressing our gratitude to all those who contributed to this endeavour, we must mention that it was a global effort. So while, on the one hand, we had some of our revered teachers and mentors contribute chapters, we also had distinguished international authors, each adding a unique perspective for the reader. Most of the authors are experts in the areas of their contributions, and this reflects in their balanced and valuable opinions. We would also like to concede that drawing of experts from multiple sources does become a challenge in maintaining timelines.

However, every effort has been made to keep the text as updated and contemporary up to the point that we handed over our manuscript to the publisher. We hope that this book will be an asset for all of you who seek answers to questions that arise while you manage neurological emergencies.

New Delhi, India

Mamta Bhushan Singh  
Rohit Bhatia

---

# Contents

<b>1</b>	<b>Neurological Emergencies in Tropical Infections</b> . . . . .	<b>1</b>
	Ravindra Kumar Garg and Imran Rizvi	
<b>2</b>	<b>Autoimmune Encephalitis</b> . . . . .	<b>21</b>
	Saiju Jacob and Angela Vincent	
<b>3</b>	<b>Acute Demyelinating Emergencies</b> . . . . .	<b>45</b>
	Jean-Christophe Ouallet	
<b>4</b>	<b>Acute Non-traumatic Myelopathies</b> . . . . .	<b>65</b>
	K. Venkatraman, N. Tamil Pavai, and R. Lakshmi Narasimhan	
<b>5</b>	<b>Neuromuscular Emergencies</b> . . . . .	<b>105</b>
	Kavita Mohindra Grover and Naganand Sripathi	
<b>6</b>	<b>Movement Disorders in the Emergency</b> . . . . .	<b>133</b>
	Madhuri Behari and Vibhor Pardasani	
<b>7</b>	<b>Neurological Emergencies in the Immunocompromised Population</b> . . .	<b>157</b>
	Ajitesh Ojha and Saša A. Živković	
<b>8</b>	<b>Neurological Emergencies in Pregnancy</b> . . . . .	<b>171</b>
	Sucharita Ray, Rohit Bhatia, and Mamta Bhushan Singh	
<b>9</b>	<b>Acute Neurological Emergencies in Drug Abusers in India</b> . . . . .	<b>189</b>
	Boby Varkey Maramattom	
<b>10</b>	<b>Neuro-Oncology Emergencies Induced by Chemotherapy</b> . . . . .	<b>197</b>
	Indranil Ghosh and Sameer Bakhshi	
<b>11</b>	<b>Neurosurgical Interventions in Neurological Emergencies</b> . . . . .	<b>207</b>
	Sandeep Mohindra, Rahul Gupta, and Kamal Verma	
<b>12</b>	<b>Toxins and the Nervous System</b> . . . . .	<b>229</b>
	Pradeep P. Nair, Jayantee Kalita, and Usha K. Misra	
<b>13</b>	<b>The Problem of Death in Critical Care Medicine</b> . . . . .	<b>251</b>
	David W. Crippen	

---

## About the Editors

**Mamta Bhushan Singh** has been a faculty member at the All India Institute of Medical Sciences, New Delhi, since 2002 and is currently a professor at the Department of Neurology. Her work is mainly focused on reducing the burden of untreated epilepsy in India. Over the past decade, she has published her research in international journals and made presentations at numerous international meetings. Her ongoing initiative, which provides epilepsy care to rural Indian patients through a mobile clinic on the Lifeline Express, has been highly successful. The American Academy of Neurology selected her as the 2016 Viste Patient Advocate of the Year in recognition of her community work on epilepsy.

**Rohit Bhatia** has been a faculty member at the All India Institute of Medical Sciences, New Delhi, since 2003 and is currently a professor at the Department of Neurology. His keen interest in stroke took him to the University of Calgary, Canada, where he completed a Fellowship in Cerebrovascular Disorders from the Calgary Stroke Program in 2010. He has been working towards improving stroke programmes ever since, and his efforts were recognized by the American Academy of Neurology with the ‘Safety and Quality’ Award in 2015. Dr Bhatia has published extensively in Indian and international journals, not only on stroke but also on demyelinating disorders, neuromuscular diseases, headache and stem cell therapy. He recently headed the group appointed by the Government of India for formulating the CNS TB guidelines for managing extrapulmonary TB. Most of his current research is in the field of demyelinating diseases and stroke, including an investigation of the interplay between coronary artery disease and ischemic stroke in Indian patients.



---

## Contributors

**Sameer Bakhshi** Department of Medical Oncology, Dr B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

**Madhuri Behari** Consultant Neurologist, Fortis Hospital, Vasant Kunj, New Delhi, India

**Rohit Bhatia** Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

**David Crippen** Department of Critical Care Medicine, Scaife Hall, University of Pittsburgh, Pittsburgh, PA, USA

**Ravindra Kumar Garg** Department of Neurology, King George Medical University, Lucknow, Uttar Pradesh, India

**Indranil Ghosh** Department of Medical Oncology, Dr B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

**Kavita Mohindra Grover** Department of Neurology, Henry Ford Hospital and Wayne State University, Detroit, MI, USA

**Rahul Gupta** Department of Neurosurgery, Fortis Hospital, Noida, India

**Saiju Jacob** Department of Neurology, University Hospitals Birmingham and Neuroimmunology Clinical Lead, University of Birmingham, Birmingham, UK

**Jayantee Kalita** Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

**Boby Varkey Maramattom** Aster Medcity Hospital, Kochi, Kerala, India

**Usha K. Misra** Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

**Sandeep Mohindra** Department of Neurosurgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

**Pradeep P. Nair** Additional Professor, Department of Neurology, JIPMER, Puducherry, India

**R. Lakshmi Narasimhan** Institute of Neurology, Madras Medical College, Chennai, Tamil Nadu, India

**Ajitesh Ojha** Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

**Jean-Christophe Ouallet** Department of Neurology, Multiple Sclerosis Center, University of Bordeaux, Hôpital Pellegrin-Tripode, Bordeaux Cedex, France

**Vibhor Pardasani** Department of Neurology, Seven Hills Hospital, Mumbai, Maharashtra, India

**N. Thamil Pavai** Institute of Neurology, Madras Medical College, Chennai, Tamil Nadu, India

**Sucharita Ray** Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

**Imran Rizvi** Department of Neurology, King George Medical University, Lucknow, Uttar Pradesh, India

**Mamta Bhushan Singh** Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

**Naganand Sripathi** Department of Neurology, Henry Ford Hospital and Wayne State University, Detroit, MI, USA

**K. Venkatraman** Institute of Neurology, Madras Medical College, Chennai, Tamil Nadu, India

**Kamal Verma** Department of Neurosurgery, Asian Institute, Faridabad, Haryana, India

**Angela Vincent** Nuffield Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, UK

**Saša A. Živković** Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

# Neurological Emergencies in Tropical Infections

# 1

Ravindra Kumar Garg and Imran Rizvi

---

## Introduction

Neurological emergencies in tropical infections are often encountered in emergency departments of India and many resource-constrained countries. Serious tropical infections often lead to mortality and severe morbidity amongst survivors [1]. Many of these infections can be rapidly fatal if not recognized and treated promptly; therefore, it is important for emergency physicians and neurologist especially those working in tropics to be well versed with recognition and management of these infections. The threat from neurological infectious diseases increases further because of increasing prevalence of people infected with human immune deficiency virus (HIV) infection.

---

## Clinical Approach to Tropical Infections in Neurological Emergencies

Tropical infections can present to emergency department with a variety of symptoms and the emergency physician should consider common differential diagnosis for these symptoms. All patients should undergo detailed history regarding onset, duration and progression of symptoms. History of constitutional symptoms like fever, weight loss, loss of appetite should be especially asked for; enquiry should be made regarding contact with tuberculosis, high risk behaviour and drug abuse (Table 1.1). General examination should be done to look for skin rashes, lymph node enlargement, evidence of sinusitis, ear infections, dental caries, skin and soft-tissue infections. Neurological examination should screen higher functions, cranial nerves, motor and sensory functions along with signs of meningeal irritation. Acute disseminated encephalomyelitis, an immune-mediated demyelinating syndrome, can cause clinical manifestations mimicking many of these tropical infections of brain.

---

R. K. Garg (✉) · I. Rizvi

Department of Neurology, King George Medical University, Lucknow, Uttar Pradesh, India

© The Author(s) 2019

M. B. Singh, R. Bhatia (eds.), *Emergencies in Neurology*,  
[https://doi.org/10.1007/978-981-13-7381-7\\_1](https://doi.org/10.1007/978-981-13-7381-7_1)

**Table 1.1** Infectious causes of common neurological symptoms in tropics

Symptoms	Causes
Headache	Bacterial meningitis Tuberculous meningitis Fungal meningitis Brain abscess Encephalitis
Fever with altered sensorium	Bacterial meningitis Tuberculous meningitis Fungal meningitis Brain abscess Viral encephalitis
Seizures/status epilepticus	Neurocysticercosis Bacterial meningitis Tuberculous meningitis Fungal meningitis Viral encephalitis
Vision loss	Tuberculous meningitis (optochiasmatic tuberculosis) Neurocysticercosis (retinal cyst) Cytomegalovirus retinitis
Cranial neuropathies	Tuberculous meningitis Fungal infections Bacterial meningitis
Paraplegia/quadriplegia	Spinal tuberculosis Spinal epidural abscess Dengue myositis Dengue related hypokalemia Pyomyositis Diphtheria Polio-myelitis Botulism
Extra pyramidal syndromes/dystonias	Japanese encephalitis

## Meningitis

Meningitis refers to inflammation of membranes surrounding the brain and spinal cord; this includes inflammation of arachnoid, pia mater and surrounding cerebro-spinal fluid (CSF). Meningitis can be caused by a variety of infectious and non-infectious causes, including bacterial, tuberculosis, viral, fungal, neoplastic, toxic and autoimmune.

## Bacterial Meningitis

The most common bacteria causing community acquired bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis* [2]. The classical clinical features of meningitis include the triad of fever, neck rigidity and altered sensorium. Although recent studies have pointed out that the classical triad may not be present

in all the patients. The classical triad was found to be present in only 44% of bacterial meningitis in a recent study [2]. However, about 95% of patients had two of the four features of headache, fever, neck stiffness and altered mental status [2]. Elderly, neonates and immunocompromised patients often pose diagnostic challenges as they may not show the classical clinical features. Important physical signs associated with meningitis are *nuchal rigidity*, *Kernig's sign* and *Brudzinski's sign*. *Kernig's sign* is elicited by flexing the hip and extending the knee; a Kernig's sign is said to be positive when such manoeuvre elicits pain in the back and legs. *Brudzinski's sign* is said to be positive when passive flexion of neck in supine position leads to flexion of hip joints.

CSF examination remains the key investigation in making a diagnosis of bacterial meningitis [3]. One of the important issues faced by the emergency physicians during management of meningitis is whether to go for neuroimaging before doing a lumbar puncture or not? [3]

It has been suggested that it is reasonably safe to go for lumbar puncture before neuroimaging if the patient does not have any of the following conditions:

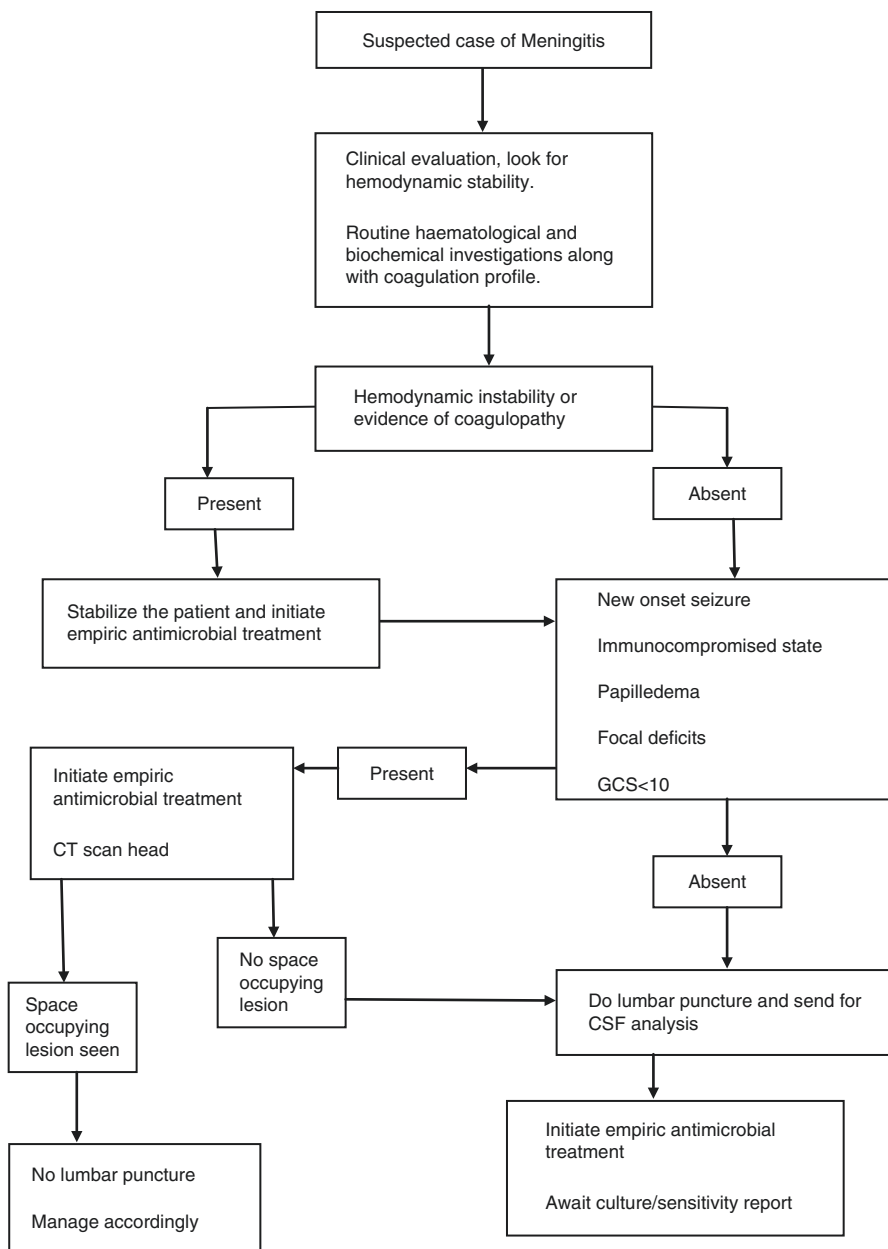
1. new onset seizure,
2. immunocompromised state,
3. signs suggestive of space occupying lesion (papilledema or focal neurological signs) and
4. moderate to severe impairment of consciousness [3, 4].

Classically described findings in CSF of bacterial meningitis are elevated opening pressure, elevated CSF protein, low levels of CSF glucose (<40 mg/dL; CSF glucose/blood glucose <0.4) and CSF leucocyte count >1000/mL with predominant neutrophils. CSF gram staining has a variable sensitivity of 50–90% but the specificity of positive gram stain is nearly 100% [2] (Fig. 1.1).

As bacterial meningitis can rapidly be fatal, empiric antimicrobial therapy should be started as soon as possible. Therapy can be further tailored when the results of culture and sensitivity are available [3–5]. Patients with bacterial meningitis should also receive intravenous dexamethasone in a dosage of 10 mg every 6 h for 4 days; dexamethasone should be started before or along with first dose of antibiotic [3] (Table 1.2). The reader is requested to refer to the chapter on bacterial meningitis for more details.

## Tuberculous Meningitis

Tuberculous meningitis (TBM) is one of the most common CNS infections especially amongst people living in tropics. TBM can kill or severely disable about 50% of affected patients [6]; therefore, it is especially important for emergency physicians and neurologists to recognize and treat this potentially fatal condition promptly. TBM is caused by *Mycobacterium tuberculosis*. The pathogenesis of TBM is usually explained by a two-step model which was first proposed by Rich and McCordock. As per this model, tuberculous granulomas (or Rich foci) form on



**Fig. 1.1** Flow chart for evaluation of a suspected case of meningitis

**Table 1.2** Initial empiric antibiotic therapy for bacterial meningitis [3–5]

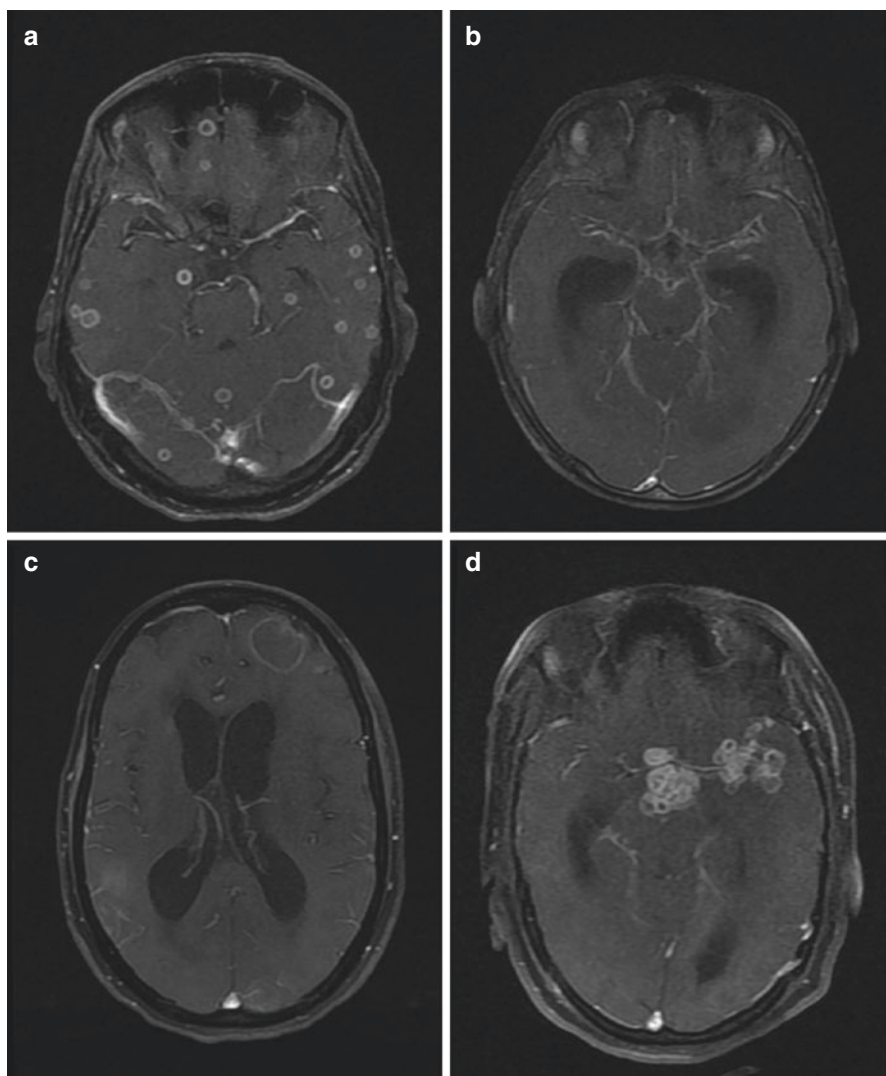
Age	Intravenous antimicrobial agent	Dosage
Adult <50 years	Ceftriaxone	2 g every 12 h
	Or	
	Cefotaxime	2 g every 8 h
	Plus	
	Vancomycin	1 g every 12 h
Adult >50 years Or risk factors like alcohol abuse, immunocompromised, recent head injury or CSF leak	Ceftriaxone	2 g every 12 h
	Or	
	Cefotaxime	2 g every 8 h
	Plus	
	Vancomycin	1 g every 12 h
	Plus	
	Ampicillin	12 g/day divided every 4 h

meninges and release the bacteria in subarachnoid space. TBM can affect all age groups; patients infected with HIV are at increased risk of developing TBM.

Early symptoms of TBM are often non-specific and include malaise, fever, weight loss, gradual onset headache. Followed by this intensity of headache increases, and confusion, coma and death occur if left untreated [6, 7]. Neck rigidity may be absent early in the course, and cranial nerve palsies, monoplegia, hemiplegia and paraplegia may develop later in the course [7].

Classical CSF findings include raised WBC count with predominant lymphocytic reaction, CSF protein levels are raised (0.8–4 g/L); CSF glucose is low and usually less than 50% of blood glucose [7]. Early in the course of disease an increase in CSF polymorphonuclear cell count may be observed but they are replaced by lymphocytes over a period of few weeks. Definite diagnosis of TBM requires demonstration of tuberculous bacilli in CSF either by microscopy or by culture [7]. CSF Ziehl–Neelsen staining and microscopy is limited by the fact that yield is often low; yield can be increased by draining large volume of CSF and doing meticulous microscopy. But the sensitivity of microscopy seldom reaches 60% [8]. Culture positivity is also not very high in TBM; rates of culture positivity range from 25 to 70% [7] and the culture takes a long time to grow the tuberculous bacilli. Newer diagnostic methods like polymerase chain reaction (PCR) can be expensive and not widely available in resource poor settings. GeneXpert can be used to quickly help the clinician in making a diagnosis and also ascertaining resistance, but sensitivity in CSF is between 60 and 70%. The absence of positivity on this test does not rule out the diagnosis of TBM and clinical judgement is paramount so as not to miss this diagnosis.

Contrast enhanced CT scan of the head is helpful in supporting the diagnosis and is more commonly available and should be performed in all cases of suspected TBM. Magnetic resonance imaging (MRI) may be better than computed tomography (CT) scan in determining the tuberculous pathology [9]. MRI can demonstrate meningeal enhancement, hydrocephalous, basal exudates, optochiasmatic arachnoiditis, tuberculomas and infarcts (Fig. 1.2).



**Fig. 1.2** Classical MRI findings in tuberculous meningitis; post-contrast T1 image shows (a) multiple tuberculomas (b) basal exudates with hydrocephalous (c) hydrocephalous with tuberculoma in left frontal lobe (d) optochiasmatic tuberculomas



**Table 1.3** Anti-tuberculous drugs and their dosage in TBM

Drug	Route	Dose (mg/kg/day)	Maximum dose (mg)
Isoniazid	Oral	5	300
Rifampicin	Oral	10	600
Pyrazinamide	Oral	25	2000
Streptomycin	Intramuscular	20	1000
Ethambutol	Oral	15	1200

The World Health Organization (WHO) recommends giving four drugs isoniazid, rifampicin, pyrazinamide and intramuscular streptomycin or ethambutol for 2 months followed by isoniazid and rifampicin for 7 months [10] (Table 1.3). Most experts however suggest using four-drug ATT for the first 2 months and three-drug ATT (rifampicin, isoniazid and pyrazinamide) for the next 10 months. All patients should also receive adjunctive corticosteroids for a period of 8 weeks, using intravenous dexamethasone (0.4 mg/kg body weight per day and then tapered off decreasing 0.1 mg/kg every week); oral dexamethasone should be given for the next 4 weeks (starting at a total of 4 mg/day and decreasing by 1 mg each week) [11]. Anticonvulsants and cerebral decongestion should be given to the patients who developed seizures or features of raised intracranial tension, respectively [11]. Ventriculoperitoneal shunting should be performed for symptomatic patients with hydrocephalous if they do not respond to conservative measures or if the hydrocephalous is non-communicating [12].

## Fungal Meningitis

Fungal infections of CNS have high mortality and morbidity [13]. Fungal infections of CNS are increasing in prevalence due to increasing population of immunocompromised hosts as a result of HIV pandemic. Fungal infections of CNS can present in a variety of ways including meningitis, encephalitis, space occupying lesions, cranial neuropathies, vascular and spinal cord syndromes [14]. Fungal meningitis is the most common clinical presentation amongst them. Most common fungi causing meningitis are *Cryptococcus*, *Coccidioides*, *Blastomyces*, *Paracoccidioides*, *Sporotrichum*, *Histoplasma* and *Candida* [14]. Clinical features of fungal meningitis are headache, fever, altered sensorium, personality changes, cranial nerve palsies, hydrocephalous, papilledema and seizures [14].

CSF examination classically shows lymphocytic or monocytic pleocytosis. *Aspergillus* and *Blastomyces* meningitis can show neutrophilic predominance. *Coccidioidomycosis* infection causes CSF eosinophilia [13]. CSF protein is elevated and glucose is low. India ink preparation or fungal culture can be used for demonstration of organisms; but they usually require large volume of CSF to do so. The cryptococcal polysaccharide antigen detection test has got good sensitivity and specificity. The CSF complement fixation antibody test has a reported sensitivity of 75% and specificity of 100% for *Coccidioidomycosis* meningitis [15]. The medical management for cryptococcal meningitis is outlined in Table 1.4.

**Table 1.4** Antifungal therapy for cryptococcal meningitis [14]

Non-HIV-infected, non-transplant hosts
<i>Induction phase</i>
Amphotericin B 0.7–1.0 mg/kg/day IV for at least 4 weeks
Plus
Flucytosine 100 mg/kg/day orally in four divided doses for 4 weeks
Therapy can be prolonged for 6 weeks in case of neurological complications
<i>Consolidation phase</i>
Fluconazole 400 mg/day for 8 weeks
HIV-infected individuals
<i>Induction phase</i>
Amphotericin B 0.7–1.0 mg/kg/day IV for at least 2 weeks
Plus
Flucytosine 100 mg/kg/day orally in four divided doses for 2 weeks
<i>Consolidation phase</i>
Fluconazole 400 mg/day for 8 weeks
Organ transplant recipient
<i>Induction phase</i>
Liposomal amphotericin B (3–4 mg/kg/day IV) or amphotericin B lipid complex (5 mg/kg/day IV)
Plus
Flucytosine (100 mg/kg/day in four divided doses) for at least 2 weeks
<i>Consolidation phase</i>
Fluconazole (400–800 mg [6–12 mg/kg]/day orally) for 8 weeks

CSF diversion procedure should be done in patients who develop hydrocephalous. Ventriculostomy should be done till CSF culture is sterile followed by ventriculoperitoneal shunt.

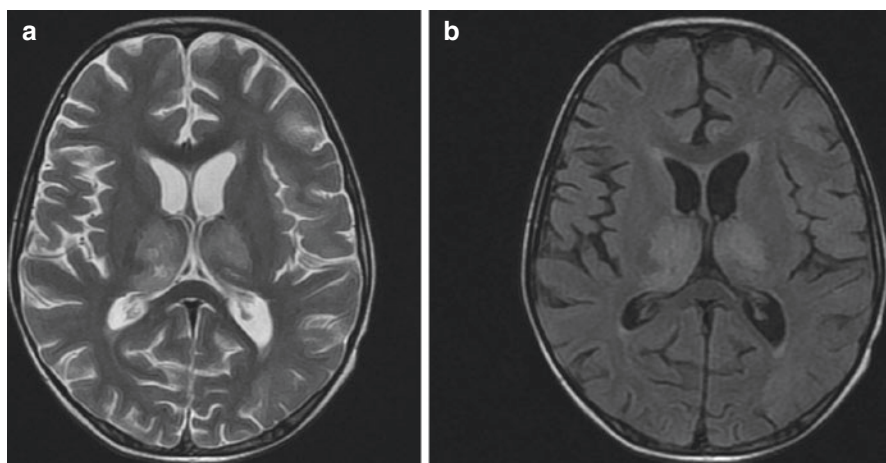
## Encephalitis/Encephalopathy

Encephalitis refers to inflammation of brain parenchyma. The common encephalitis/infective encephalopathies encountered in emergency rooms of tropics include Japanese encephalitis (JE), herpes simplex virus (HSV) encephalitis, cysticercotic encephalitis and cerebral malaria.

### Japanese Encephalitis (JE)

JE virus (JEV) is one of the most common causes of acute encephalitis syndrome in northern India [16]. JEV belongs to the group flaviviridae; culex mosquito transmits the virus between animal and human host. Nearly 30% of the admitted patients of JE die and about 50% of the survivors are left with neurological sequelae [17].

JE most commonly occurs in children, although all age groups can be infected if JEV is recently introduced in an area. Most JEV infections in humans are apparently asymptomatic. Spectrum of symptomatic illness varies from non-specific febrile illness to aseptic meningitis to severe encephalitis [17]. Most of the patients



**Fig. 1.3** Characteristic MRI findings in Japanese encephalitis; (a and b) T2 and FLAIR images show hyperintensities in bilateral thalami

develop initial non-specific illness in the form of fever, headache, rigors, malaise and abdominal symptoms. Development of encephalitis syndrome is characterized by altered sensorium, abnormal behaviour, seizures, hemiplegia, quadriplegia and coma. Movement disorders are commonly seen in JE patients as they recover from coma [17]. Movement disorders commonly seen in JE are masking of face, reduced blinking, akinesia, rigidity, tremors and dystonia.

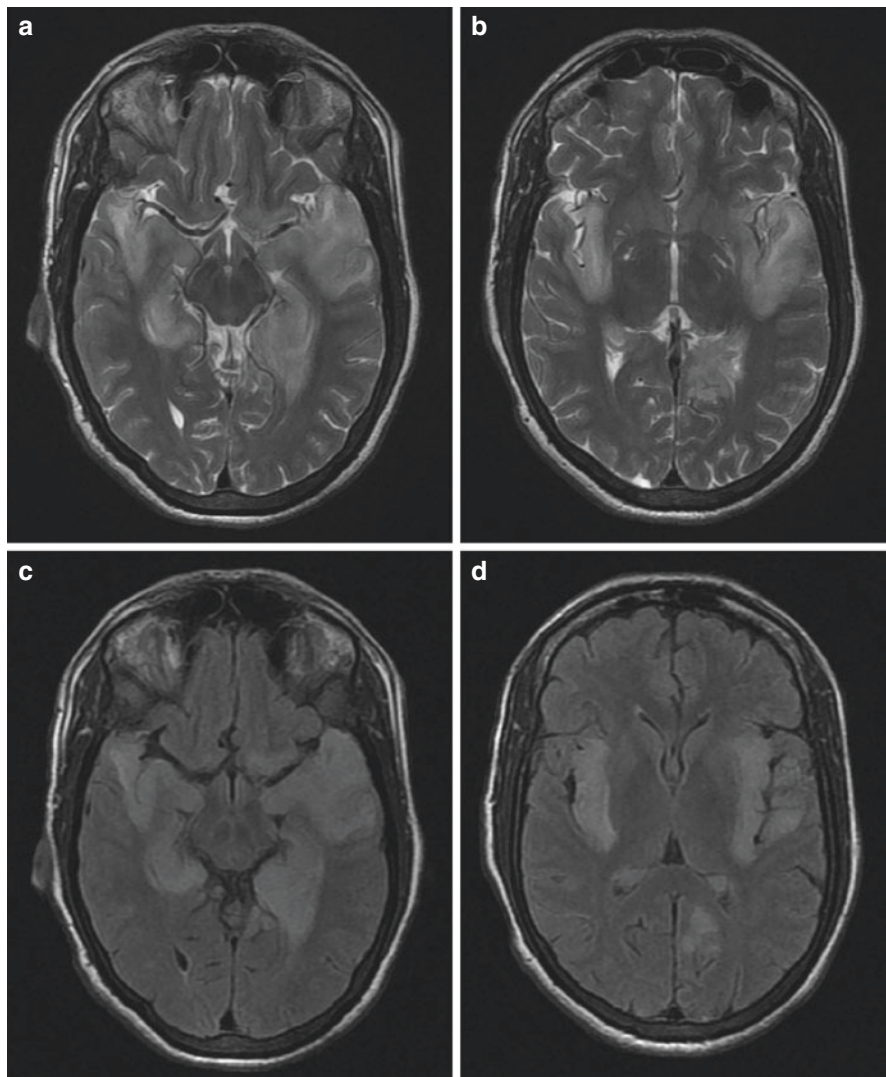
CSF examination generally shows moderate increase in protein, normal sugar and moderate amount of lymphocytic pleocytosis. IgM capture enzyme linked immunosorbent assay (ELISA) to detect antibodies in CSF has high sensitivity and specificity. MRI is more sensitive in detecting lesions of JE. MRI may show lesions of thalamus, basal ganglia, substantia nigra, cerebellum, pons and cerebral cortex. These lesions are hypointense on T1 and hyperintense on T2 and FLAIR. Lesions of bilateral thalamus can be haemorrhagic [16] (Fig. 1.3).

At present no specific anti-viral therapy is available against JEV. Management is supportive and includes antipyretics, anticonvulsants, prevention of aspiration and bed sores, etc.

## Herpes Simplex Encephalitis

Herpes simplex encephalitis (HSE) is considered to be the commonest cause of viral encephalitis in the western world but it is also not uncommon in tropics. HSV-1 accounts for majority of the cases of HSE [18]. HSE affects all ages and both sexes. Preferential involvement of frontotemporal, cingulate and insular cortex is considered to be the pathological hallmark of HSE. Clinical features are not specific and include acute onset of flu like illness, headache, altered mental status, seizures, amnesia, recent memory loss, personality changes, focal deficits and coma [18].

MRI remains the imaging procedure of choice for diagnosis of HSE. MRI typically shows signal intensity changes in the medial aspects of the temporal lobes, orbital surfaces of the frontal lobes, insular cortex and cingulate gyrus [18] (Fig. 1.4). EEG may show periodic focal temporal spikes repeating at regular interval of 2–3 s. CSF analysis typically shows lymphocytic pleocytosis, elevated protein and normal sugar. In some cases of HSE red blood cells can be seen on CSF examination. CSF polymerase chain reaction (PCR) for HSV is very helpful in diagnosis as it carries high sensitivity (90%) and specificity (100%) [18].



**Fig. 1.4** Characteristic MRI findings in *Herpes simplex* encephalitis; T2 (a and b) and FLAIR (c and d) images show hyperintensities in bilateral medial temporal lobe and insular cortex

Acyclovir in a dose of 10 mg/kg every 8 h should be started as soon as diagnosis of HSE is suspected; early initiation of therapy reduces mortality. Therapy should be continued for at least 14 days on confirmation of diagnosis. It is prudent to monitor side effects and keep a close watch on renal functions during the course of treatment. Supportive treatment in the form of anticonvulsants, antipyretics and management of raised intracranial pressure should be done as required.

## Cerebral Malaria

Four species of plasmodium, namely *P. falciparum*, *P. vivax*, *P. ovale* and *P. Malariae* cause malaria. Cerebral malaria is most often caused by *P. falciparum* and sometimes by *P. vivax*. Cerebral malaria is defined as ‘unarousable coma (GCS < 10 or Blantyre coma scale < 3) with presence of asexual parasites in blood and in which locally prevalent encephalitis and meningitis has been ruled out by appropriate tests’. However, this definition is more true of research purposes for practical purpose any patient with malaria having altered sensorium should be treated as cerebral malaria until proven otherwise [19]. The presence of malarial retinopathy can be used to differentiate children in coma caused by *Plasmodium falciparum* from those with other causes of altered mental status.

The clinical features of cerebral malaria are fever, abnormal sensorium, seizures, abnormal posturing and coma. Physical signs may be retinal haemorrhages, papilloedema, extensor plantar responses, increased muscle tone and sometimes meningeal signs may be present [19]. The mortality associated with cerebral malaria remains high despite meticulous treatment. Survivors may develop neurological sequelae like aphasia, hemiplegia, ataxia and deafness [20].

Diagnosis of cerebral malaria is mainly clinical and is confirmed by demonstration of parasites in peripheral blood; parasite demonstration is usually done by examining thick and thin blood smear. Other useful tests are antigen detection using rapid malaria antigen test and quantitative buffy coat test (QBC). CSF examination in cerebral malaria is usually normal.

Cerebral malaria is a medical emergency and treatment should be started promptly. Treatment includes antimalarial drugs plus supportive care in the form of maintaining hydration, antipyretics and management of other associated complications like aspiration, hypoglycaemia, seizures and anaemia. Recent data strongly suggest that parenteral artesunate is superior to quinine and parenteral artesunate is the treatment of choice for severe falciparum malaria (Table 1.5).

## Neurocysticercosis

Patients with neurocysticercosis can present to emergency department either with acute seizures or acute encephalopathy. Neurocysticercosis (NCC) is the most common parasitic disease of the central nervous system. It is caused by larval stage of the pork tapeworm *Taenia solium*. NCC is endemic in most of the developing

**Table 1.5** Treatment of cerebral malaria

Drug	Dosage
Artesunate	2.4 mg/kg IV stat Followed by 2.4 mg/kg IV at 12 h, 24 h and then daily
Or Artemether	3.2 mg/kg IM stat Followed by 1.6 mg/kg/day IM
Or Quinine	20 mg/kg over 4 h IV infusion Followed by 10 mg/kg IV every 8 h

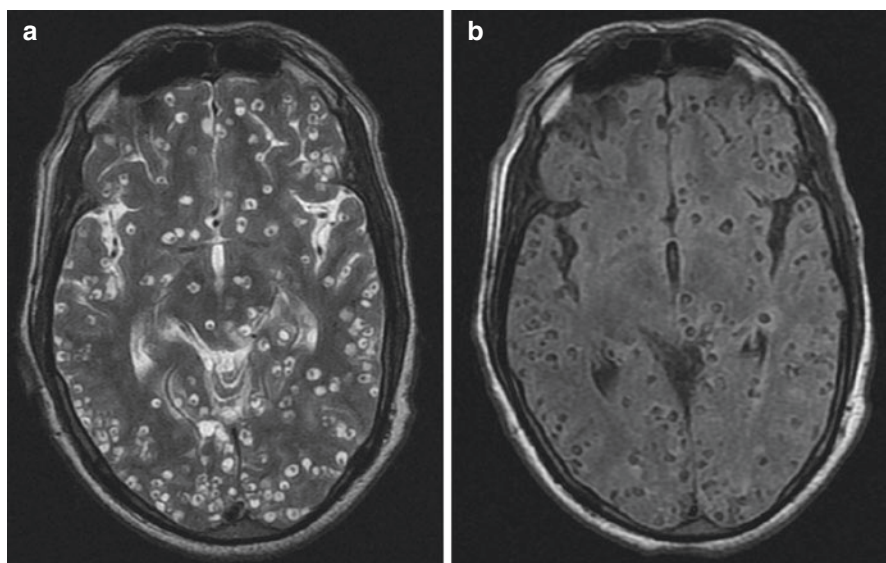
countries. It is one of the most common causes of the seizure in the developing world [21]. Clinical manifestations of NCC may vary from asymptomatic disease to severe encephalitis and death [21].

NCC is often regarded as the 'great imitator' because it can mimic any neurological presentation [22]. Many factors like number, size, location of lesions and host immune response determine the clinical presentation of NCC [22]. Seizures are the most common presentation of NCC. About 92% of patients with intraparenchymal lesions and 74% with mixed intra- and extraparenchymal lesions present with seizures [23]. Patients can present with focal seizures with or without secondary generalization, status epilepticus or post-seizure focal neurological deficit [23]. Cysticercotic encephalitis is a life threatening form of disease which occurs mainly in children and adolescents and is the result of widely disseminated small intraparenchymal cysts. The features of cysticercotic encephalitis are raised intracranial pressure, unconsciousness and seizures [24]. Other presenting features of NCC can be dementia, muscular pseudohypertrophy, focal deficits of vascular origin and spinal cord syndromes [23].

The diagnosis of NCC is usually made by neuroimaging. CT scan has got good sensitivity for detection of NCC except for posterior fossa lesions, lesions near bony surfaces and intraventricular lesions [25]. For detection of intraventricular cysticercosis, brainstem cysts and small cysts located over the convexity of cerebral hemispheres MRI is the imaging modality of choice [25]. Imaging characteristics of NCC depend upon its stage. Vesicular stage shows small and rounded lesions with no perilesional oedema or contrast enhancement, tapeworm scolex can be visualized inside the lesion (hole-with-dot). Colloid cyst stage has poorly defined borders, is surrounded by oedema and shows ring and nodular contrast enhancement. Granular stage is recognized by nodular hyperdense lesions surrounded by oedema after contrast enhancement. Calcified stage appears as hyperdense nodule on plain CT scan [25] (Fig. 1.5).

Management of NCC requires a combination of anti-epileptic drugs, cysticidal drugs and steroids. Cysticidal drug albendazole is given in a dose of 15 mg/kg/day [26]. Cysticidal drugs should not be used in the management of cysticercotic encephalitis as they may exacerbate the syndrome of intracranial hypertension [26]. Patients of cysticercotic encephalitis are usually treated with steroids, mannitol and anti-epileptic drugs. Treatment of NCC is summarized in Table 1.6 [21, 22].





**Fig. 1.5** T2 and FLAIR MRI images show multiple neurocysticercosis (a) T2 image, (b) FLAIR image

**Table 1.6** Treatment approach for neurocysticercosis [21, 22]

<i>Intraparenchymal neurocysticercosis</i>	
Cysticercotic encephalitis	Anti-cysticidal drugs should <i>not</i> be used Symptomatic management of raised intracranial tension (steroids, mannitol, acetazolamide, diuretics) and seizure (anti-epileptic drugs)
Calcified granulomas only	Anti-cysticidal drugs <i>not</i> required Symptomatic management of seizures using anti-epileptic drugs
One or several vesicular or degenerative cysts	Albendazole 15 mg/kg/day or praziquantel 100 mg/kg in three equal doses along with steroids Symptomatic management of seizures using anti-epileptic drugs
<i>Extraparenchymal Neurocysticercosis</i>	
Basal subarachnoid neurocysticercosis	Albendazole 15 mg/kg/day for $\geq 1$ month, with high doses of steroids
Intraventricular neurocysticercosis	Endoscopic excision of lesion, ventriculoperitoneal shunt placement
Sylvian fissure neurocysticercosis	Albendazole 15 mg/kg/day for $\geq 1$ month, with high doses of steroids Surgical excision can be considered
<i>Neurocysticercosis at other sites</i>	
Ocular cysts	Surgical excision Avoid anti-cysticidal drugs
Spinal cysts	Surgical excision Anti-cysticidal drugs and steroids can be used

## Brain Abscess

Brain abscess is a difficult clinical problem with high mortality rate despite advances in medical and surgical management [27]. The causative organisms of brain abscess include bacteria, mycobacteria, fungi and protozoa [27]. Common risk factors for development of brain abscess are sinusitis, mastoiditis, dental infections, head trauma, neurosurgical procedures, endocarditis, HIV infection and treatment with immunosuppressive drugs [28]. Pathogens causing brain abscess are usually dependent upon predisposing conditions. HIV-infected patients can develop brain abscess due to *Mycobacterium tuberculosis*, *Toxoplasma gondii* and fungi. Organ transplant recipients are at risk of fungal and nocardia abscess. Patients having head trauma or neurosurgical procedures can develop abscess due to *Staphylococcus aureus* or *S. epidermidis*. Patients having endocarditis can develop abscess due to staphylococcus or streptococcus species. Mastoiditis, sinusitis and dental infections increase the risk of abscess due to streptococcus, staphylococcus, anaerobes and polymicrobial organisms [27].

Headache is the most common symptom. The classical triad of fever, headache and altered sensorium can be seen in only 20% of cases [28]. Headache increases progressively in intensity. Fever is seen in <50% of cases. Patient can present with focal or generalized seizure, aphasia, hemiparesis and visual field defects. Patients with abscess in frontal and right temporal lobe can present with behavioural disturbances [27]. Abscess in posterior fossa can present with cranial nerve palsies, gait disturbances, drowsiness due to hydrocephalous [27].

Contrast enhanced CT scan is a rapid way of diagnosing size, number and location of abscess. MRI with diffusion weighted imaging (DWI) is sensitive and specific in differentiating brain abscess from tumours [29]. On T2 weighted MRI mature abscess shows a hyperintense centre, surrounded by hypointense capsule further surrounded by hyperintense oedema. Post-contrast T1 image contrasts enhancement of capsule and a hypointense centre. Brain abscess shows restricted diffusion on DWI MR images (Fig. 1.6).

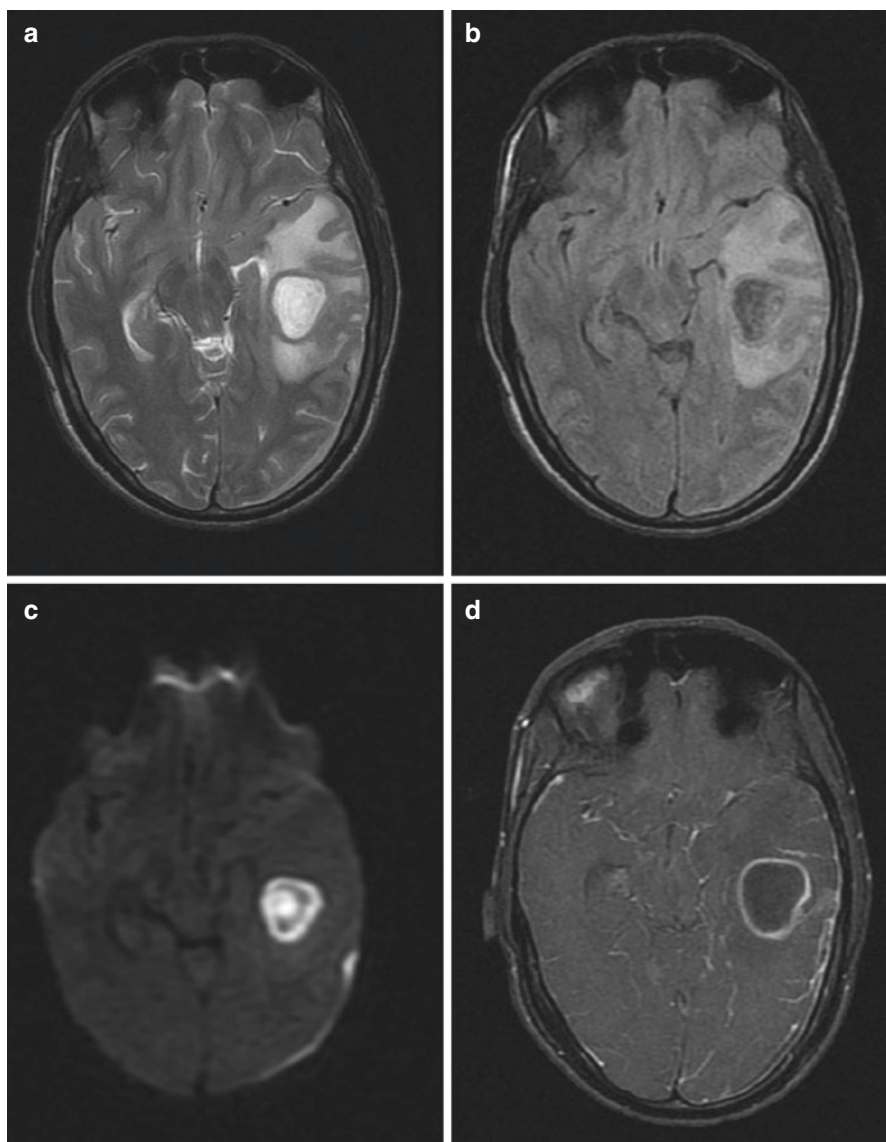
Management of brain abscess involves high dose parenteral antibiotics plus neurosurgical drainage. Medical therapy alone is not sufficient and should be offered to only those patients whose abscess is not surgically accessible or to those patients whose condition is too critical for a neurosurgical procedure. Stereotactic guided aspiration and drainage of abscess allow both therapeutic and diagnostic advantage. Empirical antibiotic therapy should be tailored after culture and sensitivity report of aspirated content [27]. Parenteral antibiotic should be continued for at least 6–8 weeks (Table 1.7).

---

## Spinal Tuberculosis

Spinal tuberculosis is a common form of extrapulmonary tuberculosis. Spine is the most common musculoskeletal site to develop tuberculous involvement. The term 'Pott's disease/Pott's spine' is commonly used to describe tuberculous involvement





**Fig. 1.6** Brain abscess involving left temporal lobe; (a) T2 image shows a hyperintense centre, surrounded by hypointense capsule further surrounded by hyperintense oedema. (b) FLAIR image. (c) Diffusion weighted image showing characteristic restricted diffusion. (d) Post-contrast T1 image shows contrast enhancement of capsule and a hypointense centre

of spine and the term Pott's paraplegia describes paraplegia due to spinal tuberculosis [30]. This disease is important for emergency physicians as early diagnosis and prompt treatment is necessary to prevent neurological disability [31]. Spinal involvement occurs due to haematogenous spread of *Mycobacterium tuberculosis*

**Table 1.7** Empiric antibiotic therapy for brain abscess [20]

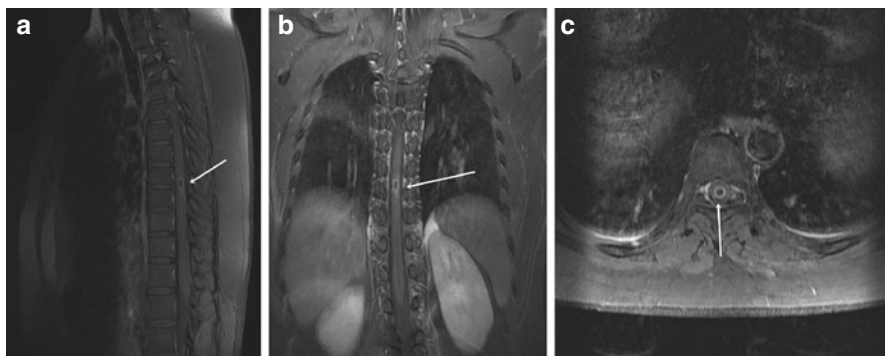
<i>Immunocompetent</i>
Cefotaxime or Ceftriaxone plus metronidazole
<i>Penetrating head injury/neurosurgical procedure</i>
Meropenem plus Vancomycin
<i>Patients with HIV infection</i>
Cefotaxime or ceftriaxone plus metronidazole, pyrimethamine and sulfadiazine; consider isoniazid, rifampicin, pyrazinamide and ethambutol to cover possible tuberculosis infection
<i>Transplant recipients</i>
Cefotaxime or ceftriaxone plus metronidazole, voriconazole and trimethoprim–sulfamethoxazole or sulfadiazine

into the dense vasculature of vertebral bodies. There is involvement of adjacent vertebra as its segmental arteries bifurcate to supply two adjacent vertebrae [30]. The most common type of involvement is paradiscal involvement, followed by anterior and central lesions of vertebral bodies.

Common clinical features of spinal tuberculosis are local pain, local tenderness, cold abscess, gibbus and spinal deformities [30]. Constitutional symptoms like malaise, weight loss, anorexia and evening rise of temperature are seen in 20–30% of patients. Back pain may be aggravated by coughing, weight bearing and spinal motion. If left untreated, then may lead to paraplegia or quadriplegia. Neurological syndrome depends upon level of vertebral involvement, cervical vertebra involvement presents with quadriplegia, thoracic spine involvement results in paraplegia and lumbar involvement may lead to cauda-equina syndrome. The site of cold abscess also depends upon level of vertebral involvement, cervical Pott's may lead to collection of pus behind prevertebral fascia leading to retropharyngeal abscess. Retropharyngeal abscess can lead to dysphagia, change in voice or respiratory distress. Involvement of thoracic spine leads to formation of paravertebral cold abscess, lumbar spine involvement leads to cold abscess formation at groin or thigh [30].

Diagnosis of spinal tuberculosis can be made in the presence of characteristic clinical and radiological findings. However, diagnosis may be delayed in cases till index of suspicion is high. Diagnosis can be further by confirmed by demonstration of acid-fast bacilli on microscopy or culture of a biopsy sample. A plain X-ray of the spine can demonstrate changes consisted with tuberculosis in about 99% of cases [30, 32]. Characteristic X-ray findings are vertebral end plates, loss of disc height, osseous destruction, new-bone formation and soft-tissue abscess [30]. MRI is the imaging procedure of choice for diagnosis of spinal tuberculosis. Apart from involvement of the vertebral bodies, disc destruction and cold abscess MRI can also demonstrate intramedullary (Fig. 1.7) or extramedullary tuberculoma and spinal cord oedema [33]. The gold standard technique for the early histopathological diagnosis of spinal tuberculosis is neuroimaging guided-needle biopsy from the affected site [32].

The management of spinal tuberculosis requires antituberculosis drugs, supportive care and surgery in specific indications. Majority of patients responds well to medical therapy, response is seen in the form of decrease in pain, neurological



**Fig. 1.7** Sagittal (a) coronal (b) and axial (c) post-contrast images showing intramedullary tuberculoma

deficit and deformity [34]. Antituberculosis drugs should be given for 9–12 months. Surgical intervention may be required in advanced cases with marked bony involvement, abscess formation or paraplegia [30].

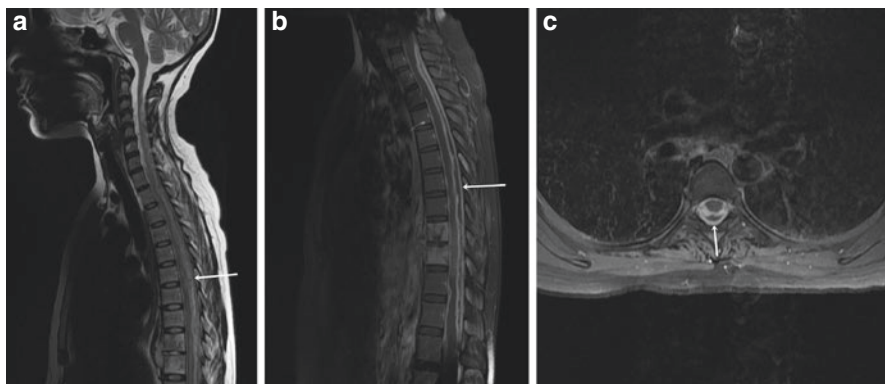
## Spinal Epidural Abscess

Spinal epidural abscess is an emergency condition which should be diagnosed and managed urgently. Common predisposing conditions for spinal epidural abscess include diabetes mellitus, HIV, alcoholism, spinal surgery or intervention, skin and soft-tissue infections, osteomyelitis, urinary tract infection and sepsis [35]. The most common organism causing spinal epidural abscess is *Staphylococcus aureus* other less common organisms include *S. Epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa* [35]. Abscess causes neurological deficit either due to direct mechanical compression of spinal cord or due to indirect septic thrombophlebitis.

The common clinical presentation of spinal epidural abscess includes fever, back pain and neurological deficit. A staging system had been proposed for progression of spinal epidural abscess, stage 1 includes back pain at the level of affection, stage 2 includes nerve root pain radiating from involved are, stage 4 includes motor dysfunction, sensory and bladder bowel involvement and stage 4 includes complete paralysis [35].

Diagnosis of spinal epidural abscess is suspected clinically and supported by imaging studies. Drainage of abscess is required for confirmation of diagnosis [35]. MRI is the imaging investigation of choice as it can localize the extent of involvement and it can also exclude other conditions (Fig. 1.8). CSF examination is not required routinely except in cases where diagnosis of associated meningitis is in question. Blood culture can be positive in about 60% of cases.

Urgent surgical drainage along with systemic antibiotics is the treatment of choice [35]. Decompressive laminectomy and debridement should be done as soon as possible. Broad spectrum antibiotics should be started pending surgery and



**Fig. 1.8** T2 (a) post-contrast T1 (b and c) showing spinal epidural abscess (white arrow) which shows hyperintense signal on T2 image and peripheral contrast enhancement in T1 image

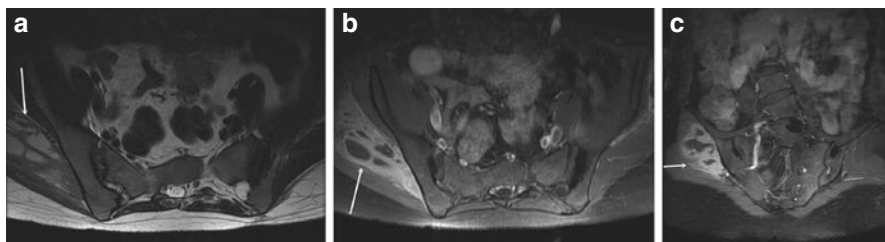
culture results, empiric antibiotic regimes should include third or fourth generation cephalosporin plus vancomycin. Medication should be modified as per culture results and should be continued for at least 4 weeks or as needed.

## Pyomyositis

Pyomyositis is a primary infection of skeletal muscles. Pyomyositis is a common occurrence in tropics although recently it had also been reported from temperate countries [36]. *Staphylococcus aureus* is the most common organism responsible for pyomyositis. Other organisms that can cause pyomyositis are *streptococci*, *Pneumococcus*, *Neisseria*, *Haemophilus*, *Aeromonas*, *Pseudomonas*, *Klebsiella* and *Escherichia* [36]. The commonly proposed pathogenesis for pyomyositis is transient bacteraemia in the setting of muscle trauma. Apart from blunt trauma to muscles overuse of muscles may be a risk factor for development of pyomyositis [36].

Pyomyositis commonly affects young, male-to-female ratio is 1.5:1 [37]. Most commonly a single muscle is involved but multiple muscle involvement can be seen in 20–40% of cases [38]. The most commonly involved muscles are thigh muscles although gastrocnemius, glutei, pectorals and biceps can also be involved frequently. Clinical features of pyomyositis are divided into three stages, namely invasive, suppurative and late stage [36]. Invasive stage is characterized by local pain and swelling along with wooden consistency. Fever and leucocytosis can be present at this stage. Usually there is no local erythema. Suppurative stage is characterized by high spikes of fever, severe local pain and tenderness. Late stage occurs if the condition remains untreated, it is characterized by sepsis, septic shock and multiorgan dysfunction [36].

For diagnosis of pyomyositis aspiration and culture of pus is a standard diagnostic method; however, pus may not be aspirated early in the disease [36]. The gold standard diagnostic procedure is muscle biopsy with culture of the tissue. Ultrasonography of the muscle can demonstrate hypoechoic areas in the muscle and



**Fig. 1.9** MRI images of a patient who presented with high grade fever and pain in hip and tenderness T2 image (a) shows bright signal in muscles on the right side. Post-contrast images (b and c) show multi-loculated peripheral rim enhancement in the same region

muscle enlargement, it can also be used to aspirate pus [36]. MRI is very sensitive in detection of pyomyositis, it can demonstrate T2 hyperintense areas with rim enhancement on post-contrast T1 images (Fig. 1.9) [39].

Antimicrobial agents should be started as soon as possible; ultrasound or CT guided percutaneous aspiration of the pus should be done [36]. Empiric antibiotics should be started awaiting culture reports. Empiric antibiotic regimen should consist of broad spectrum antibiotics covering staphylococcus, streptococcus, gram-negative bacteria and anaerobes. A commonly used empiric regimen consists of a combination of vancomycin plus an antipseudomonal carbapenem or b-lactam [36]. Antibiotic regimen can be tailored as per culture and sensitivity report later on.

## References

1. Pruitt AA. Neurologic infectious disease emergencies. *Neurol Clin.* 2012;30(1):130–59.
2. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med.* 2004;351(18):1849–59.
3. Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. *Lancet Infect Dis.* 2007;7(3):191–200.
4. Richie MB, Josephson SA. A practical approach to meningitis and encephalitis. *Semin Neurol.* 2015;35(6):611–20.
5. Mace SE. Acute bacterial meningitis. *Emerg Med Clin North Am.* 2008;26(2):281–317.
6. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. *Lancet Neurol.* 2013;12(10):999–1010.
7. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J.* 1999;75(881):133–40.
8. Thwaites GE, Chau TTH, Farrar JJ. Improving the bacteriological diagnosis of tuberculous meningitis. *J Clin Microbiol.* 2004;42(1):378–9.
9. van der Merwe DJ, Andronikou S, Van Toorn R, Pienaar M. Brainstem ischemic lesions on MRI in children with tuberculous meningitis: with diffusion weighted confirmation. *Childs Nerv Syst.* 2009;25(8):949–54.
10. WHO. Treatment of tuberculosis: guidelines. 4th ed. Geneva: World Health Organization; 2010. p. 160. <https://doi.org/10.1164/rccm.201012-1949OC>.
11. Asia CS. Index TB guidelines. New Delhi: Initiative of Central TB Division Ministry of Health and Family Welfare, Government of India Convenors; 2016. p. 63–8.

12. Bhagwati S, Mehta N, Shah S. Use of endoscopic third ventriculostomy in hydrocephalus of tubercular origin. *Childs Nerv Syst.* 2010;26(12):1675–82.
13. Rauchway AC, Husain S, Selhorst JB. Neurologic presentations of fungal infections. *Neurol Clin.* 2010;28(1):293–309.
14. Raman Sharma R. Fungal infections of the nervous system: current perspective and controversies in management. *Int J Surg.* 2010;8(8):591–601.
15. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis.* 2010;50(3):291–322.
16. Jain P, Jain A, Kumar A, et al. Epidemiology and etiology of acute encephalitis syndrome in North India. *Jpn J Infect Dis.* 2014;67(3):197–203.
17. Misra UK, Kalita J. Overview: Japanese encephalitis. *Prog Neurobiol.* 2010;91(2):108–20.
18. Schultz JC, Hilliard AA, Cooper LT, Rihal CS. Diagnosis and treatment of viral encephalitis. *Mayo Clin Proc.* 2009;84(11):1001–9.
19. Murthy JMK, Dastur FD, Khadilkar SV, Kochar DK. Rabies, tetanus, leprosy, and malaria, vol. 121. 1st ed. Amsterdam: Elsevier B.V; 2014.
20. Kochar DK, Shubhakaran, Kumawat BL, et al. Cerebral malaria in Indian adults: a prospective study of 441 patients from Bikaner, north-west India. *J Assoc Physicians India.* 2002;50:234–41.
21. Garcia HH, Nash TE, Del Brutto OH. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. *Lancet Neurol.* 2014;13(12):1202–15.
22. Garcia HH, del Brutto OH. Neurocysticercosis: updated concepts about an old disease. *Lancet Neurol.* 2005;4(10):653–61.
23. Garg RK. Classic diseases revisited Neurocysticercosis. *Postgrad Med J.* 1998;74:321–6.
24. Jain RS, Handa R, Vyas A, et al. Cysticercotic encephalitis: a life threatening form of neurocysticercosis. *Am J Emerg Med.* 2014;32(11):1444.e1–e1444.e2.
25. García HH, Del Brutto OH. Imaging findings in neurocysticercosis. *Acta Trop.* 2003;87(1):71–8.
26. Del Brutto OH. Neurocysticercosis. *Handb Clin Neurol.* 2014;121:1446–159.
27. Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med.* 2014;371(5):447–56.
28. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. *Neurology.* 2014;82(9):806–13.
29. Reddy JS, Mishra AM, Behari S, et al. The role of diffusion-weighted imaging in the differential diagnosis of intracranial cystic mass lesions: a report of 147 lesions. *Surg Neurol.* 2006;66(3):246–50; discussion 250–251.
30. Garg RK, Somvanshi DS. Spinal tuberculosis: a review. *J Spinal Cord Med.* 2011;34(5):440–54.
31. Jain AK. Tuberculosis of the spine: a fresh look at an old disease. *J Bone Joint Surg Br.* 2010;92(7):905–13.
32. Jain R, Sawhney S, Berry M. Computed tomography of vertebral tuberculosis: patterns of bone destruction. *Clin Radiol.* 1993;47(3):196–9.
33. Jung N-Y, Jee W-H, Ha K-Y, Park C-K, Byun J-Y. Discrimination of tuberculous spondylitis from pyogenic spondylitis on MRI. *AJR Am J Roentgenol.* 2004;182(6):1405–10.
34. Jutte PC, van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. *Cochrane Database Syst Rev.* 2013;5:CD004532.
35. Darouiche RO. Spinal epidural abscess. *N Engl J Med.* 2006;355:2012–20.
36. Agarwal V, Chauhan S, Gupta RK. Pyomyositis. *Neuroimaging Clin N Am.* 2011;21(4):975–83.
37. Sharma A, Kumar S, Wanchu A, et al. Clinical characteristics and predictors of mortality in 67 patients with primary pyomyositis: a study from North India. *Clin Rheumatol.* 2010;29(1):45–51.
38. Chiedozi LC. Pyomyositis. Review of 205 cases in 112 patients. *Am J Surg.* 1979;137(2):255–9.
39. Trusen A, Beissert M, Schultz G, Chittka B, Darge K. Ultrasound and MRI features of pyomyositis in children. *Eur Radiol.* 2003;13(5):1050–5.



# Autoimmune Encephalitis

# 2

Saiju Jacob and Angela Vincent

## Abbreviations

ACE-R	Addenrooke's cognitive examination-revised
ADAM	Disintegrin and metalloproteinase domain-containing protein
ADEM	Acute disseminated encephalomyelitis
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor
AZA	Azathioprine
BIRDS	Brief ictal rhythmic discharges
CASPR2	Contactin-associated protein 2
CJD	Creutzfeldt jakob disease
CSF	Cerebrospinal fluid
FDG-PET	18-fluorodeoxyglucose positron emission tomography
FLAIR	Fluid attenuation inversion recovery
GABA <sub>A</sub> R	$\gamma$ -amino-butyric acid A-receptor
GABA <sub>B</sub> R	$\gamma$ -amino-butyric acid B-receptor
GAD	Glutamic acid decarboxylase
GBS	Guillain-Barré syndrome
GCS	Glasgow coma scale
GluR	Glutamate receptor
GlyR	Glycine receptor
IST	Immunosuppressive therapy

---

S. Jacob

Department of Neurology, University Hospitals Birmingham and Neuroimmunology Clinical Lead, University of Birmingham, Birmingham, UK  
e-mail: [Saiju.Jacob@uhb.nhs.uk](mailto:Saiju.Jacob@uhb.nhs.uk)

A. Vincent (✉)

Nuffield Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, UK  
e-mail: [angela.vincent@ndcn.ox.ac.uk](mailto:angela.vincent@ndcn.ox.ac.uk)

© The Author(s) 2019

M. B. Singh, R. Bhatia (eds.), *Emergencies in Neurology*,  
[https://doi.org/10.1007/978-981-13-7381-7\\_2](https://doi.org/10.1007/978-981-13-7381-7_2)

---

IVIg	Intravenous immunoglobulin
LGII	Leucine-rich glioma inactivated protein 1
MMF	Mycophenolate mofetil
MMSE	Mini-mental state examination
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
NMDAR	<i>N</i> -methyl D-aspartate receptor
NMO	Neuromyelitis optica
PERM	Progressive encephalomyelitis with rigidity and myoclonus
PLEX	Plasma exchange
USS	Ultrasound scan
VGKC	Voltage gated potassium channel

---

## Introduction

Nearly 50 years ago, a subacute form of encephalitis was described in patients presenting with behavioural and mood changes in the absence of a known infectious or structural trigger. Post-mortem sections revealed inflammatory changes in the amygdala and hippocampus (the limbic system) [1], and hence these patients were termed to have “limbic encephalitis”. The concept of an immune mediated pathogenesis was proposed as early as 1951 [2] and years later many antibodies were identified as markers of paraneoplastic syndromes [3]. These antibodies (called Hu, Yo, Ri, Ma-2, CV-2, etc.) are directed against intracellular neuronal antigens and are thought to be surrogate markers of the tumour-associated neurological disease rather than being directly pathogenic. Cytotoxic T-cells are likely to mediate the irreversible neuronal damage. Removal of the primary tumour is the only treatment option to prevent progression and immune therapy is unlikely to be beneficial.

In contrast to these so-called classical paraneoplastic syndromes, several antibodies which are targeted against neuronal surface antigens (and hence likely to be directly pathogenic) have been discovered in the last 15 years. The antibodies bind to membrane receptors or ion channel related proteins and have been shown to alter the functional and/or surface expression of the target antigen [4]. The original description was in two patients with reversible limbic encephalitis where the target was identified as voltage gated potassium channels (VGKC) [5], although in subsequent years the exact antigenic targets have been redefined as the proteins that form part of a macromolecular complex with the VGKC, mainly the leucine-rich glioma inactivated protein 1 (LGII) and contactin-associated protein 2 (CASPR2) [6]. Other forms of immune-responsive limbic encephalitis with antibodies directed against neuronal surface antigens were described in the following 10 years with antibodies to  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPA) [7], or the  $\gamma$ -amino-butyric acid B-receptor (GABA<sub>B</sub>R) [8]. Meanwhile,



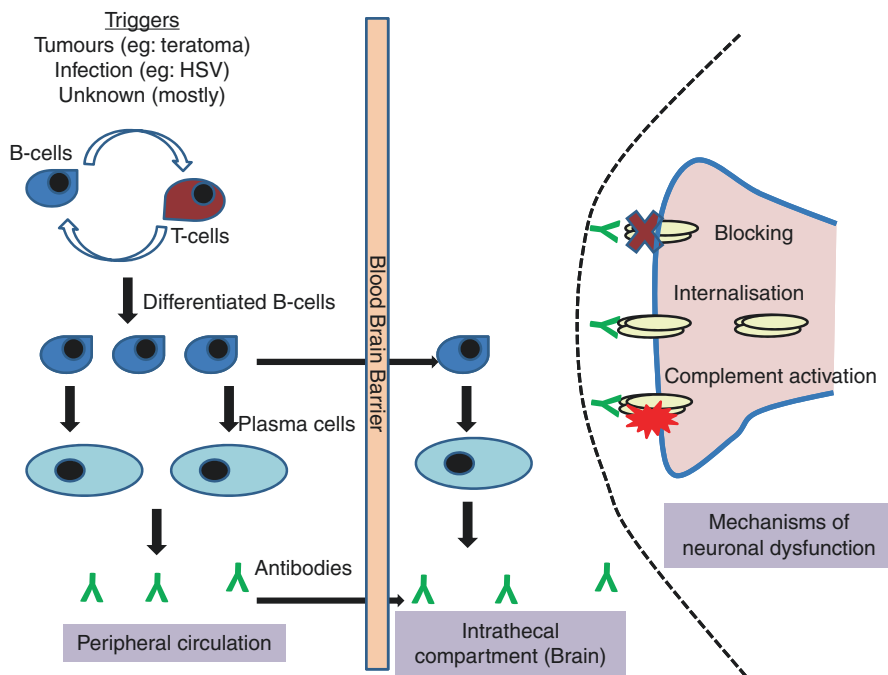
and most importantly, in 2005 [9] a novel form of autoimmune encephalitis was first described and subsequently shown to be associated with *N*-methyl D-aspartate receptor (NMDAR) antibodies [10, 11]. In addition GlyR antibodies were found in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) [12] and GABA<sub>A</sub>R antibodies were seen in patients with prominent seizures and status epilepticus [13]. Searching for these and other much rarer antibodies have now become an essential part of the differential diagnosis for patients with acute/subacute neurological disease. Patients with autoimmune encephalitis (i.e. those with antibodies against neuronal surface antigens) can be of any age, may often have no underlying tumour and have an excellent response to immunotherapy, usually with a combination of steroids, intravenous immunoglobulins or plasma exchange. The onset and severity of the symptoms and its reversibility with prompt treatment makes identification of these clinical syndromes crucial, helping to achieve substantial clinical improvement.

The chapter will focus on autoimmune encephalitis associated with the recently discovered neuronal auto-antibodies against the cell surface antigens. The so-called classical paraneoplastic syndromes secondary to the intracellular antibodies (Hu, Yo, etc.) and the acute demyelinating syndromes which can sometimes mimic an encephalitic-like illness (e.g. acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO), associated with antibodies against aquaporin-4 or myelin oligodendrocyte glycoprotein (MOG)) are beyond the scope of this chapter, and are discussed elsewhere.

---

## Pathophysiology

A clear inciting factor is elusive in the majority of patients with autoimmune encephalitis. In some patients, there is an underlying tumour (ovarian teratoma, thymoma, etc.), and more rarely a defined preceding infectious trigger (e.g. herpes simplex virus encephalitis). Irrespective of the stimulus, it is thought that there is an interaction between the T-helper cells and B-cells leading to differentiation of B-cells into plasma cells which produce the antibodies. These antibodies can leak into the intrathecal compartment due to a defective blood–brain barrier, but the B-cells can also access the central nervous system (CNS) and undergo maturation there [14] with intrathecal production of the specific antibody (Fig. 2.1). Irrespective of the origin of the antibodies, they interact with the target receptor and cause dysfunction by one or more of the three different pathophysiological mechanisms. Cross-linking and internalisation of the neuronal surface receptors will lead to loss of surface expression, and if the antibody is able to activate the complement cascade, this can also lead to cytotoxic damage with loss of the neurons. Occasionally, the antibodies directly block the function of the protein. Overall, there is loss of the receptor and/or neuronal damage leading to the neurological syndrome, although the details of where the antibodies act to cause specific features are unclear.



**Fig. 2.1** Pathophysiology of autoimmune encephalitis. Cartoon showing possible triggers and immune system changes leading to neuronal dysfunction

## Clinical Presentation

There is considerable overlap between the different phenotypes caused by these antibodies, but there are also some distinctive features which may aid in the diagnosis (Table 2.1). It is especially important to be familiar with these diagnoses since they can present in various ways as neurological emergencies (see Box 2.1).

### Box 2.1 Neurological Emergencies Raising Suspicion of Autoimmune Encephalitis

In the absence of an obvious structural, infectious, toxic or metabolic trigger, the following presentations should prompt investigations for an autoimmune encephalitis:

1. New onset seizures and status epilepticus
2. Acute delirium
3. Acute confusional state (encephalopathy)
4. Subacute memory deficits
5. Acute/subacute behavioural changes and neuropsychiatric symptoms
6. Unexplained muscle stiffness, tremor, rigidity and myoclonus

**Table 2.1** Summary of clinical features of different forms of autoimmune encephalitis (refer Abbreviations)

Antibody	Demographics	Clinical presentation	Specific features	Neuroimaging	EEG/CSF changes	Tumour association (if any)	Prognosis
NMDAR	M:F = 2:5 Age 1–85 (mean 23 years)	Psychosis, agitation, catatonia, involuntary choreoathetoid movements, oro-facial dyskinesia, seizures, dysautonomia and coma	Psychosis, preceding encephalopathy	Usually normal, but may have medial temporal lobe changes	Generalised slowing or extreme delta brush on EEG; CSF may show lymphocytic pleocytosis with raised protein	Ovarian teratoma (10–59%) Rarely testicular teratoma or SCLC	If tumour identified, better outcome on its removal. Initially can be resistant but eventually very good response to immune therapy
LGI1 (VGKC-complex)	M:F = 2:1 Mean age—65 years	Subacute encephalopathy (memory loss, confusion, seizures, behavioural changes)	Hyponatremia (60%), Faciobrachial dystonic seizures	Medial temporal lobe high signal in 40% with some developing hippocampal atrophy later; Can be normal	EEG often non-specific with diffuse slowing; CSF pleocytosis, raised protein and positive oligoclonal bands	Uncommon (<10%) Thymoma	Do not respond to anti-epileptic therapy. Slow but definite response to immunotherapy, although some patients left with mild cognitive deficits
CASPR2 (VGKC-complex)	M:F = 6:1 19–80 years (mean 57 years)	Neuromyotonia, neuropsychiatric symptoms, neuropathic pain	Morvan's syndrome	Often normal	Diffuse slowing or temporal lobe spikes on EEG; Mild lymphocytosis and raised CSF protein	0–40% Thymoma; rarely SCLC	Moderately good response to immunotherapy

(continued)

**Table 2.1** (continued)

Antibody	Demographics	Clinical presentation	Specific features	Neuroimaging	EEG/CSF changes	Tumour association (if any)	Prognosis
GABAbR	M:F = 1:1 Mean age 62 years	Subacute limbic encephalitis with seizures	Prominent seizures, especially temporal lobe onset with secondary generalisation	Increased T2W signal in medial temporal lobes	CSF lymphocytosis and mildly raised protein	Up to 50% SCLC	Good response to treatment, especially if tumour is removed completely
AMPA (GluR1/2)	F > M Mean 60 years	Limbic encephalitis with acute psychosis	Rapidly progressing	Increased T2W signal in medial temporal lobes	CSF lymphocytosis and raised protein	Breast, SCLC, thymoma (up to 70%)	Good response to treatment, but can relapse
GABAaR	M:F = 3:2 2–80 years (mean 52 years)	Seizures, status epilepticus, memory impairment, confusion, psychiatric features	Refractory seizures and status epilepticus	Cortical and subcortical T2W high signal changes	EEG often shows focal ictal activity; CSF normal or shows raised protein and lymphocytosis	Rare	Partial or complete response to immunotherapy
Glycine	M:F = 1:1 Age 1–74 years	Spasms, stiffness, myoclonus and rigidity	Stimulus sensitive startle responses	Usually normal	EEG—non-specific slowing; CSF can show pleocytosis	Rare; occasionally thymoma	Good response to immunotherapy
GAD	F > M Mean age 23 years	Subacute encephalopathy	Seizures, stiff person syndrome and cerebellar ataxia in some	Often normal	Often normal	Rare	Incomplete response; may require maintenance IVIg, anti-epileptic and anti-spastic medications

DPPX	M:F = 1:1 45–76 years (mean 60)	Confusion, agitation, tremor and seizures	Preceding diarrhoea	Subcortical white matter signal changes	EEG—non- specific slowing; CSF lymphocytosis and raised protein	None	Good response to immunotherapy
mGluR5	Very rare (case reports)	Limbic encephalitis		Medial temporal lobe or more extensive cortical T2W high signal changes		Hodgkin's lymphoma (Ophelia syndrome)	Responds to treatment of primary tumour
D2R	M:F = 1:1 Age 1.6–15 (mean 7.4 years)	Lethargy, psychiatric symptoms, involuntary movements, gait disturbance Dystonia, tremor or oculogyric crisis	Often post- vaccinal or post-infectious	Normal or basal ganglia/brain stem inflammatory changes	EEG—non- specific slowing; CSF—mild pleocytosis	None	Variable improvement with frequent motor or neuropsychiatric sequelae
IgLON5	M:F = 3:5 Age 52–76 (mean 61 years)	Non-REM and REM sleep disorder; dysarthria, dysphagia, gait instability	Chronic disease (often occurring over several years)	Normal	Normal	None	Do not respond to immunotherapy; tauopathy

P.S. Not all the conditions present as emergencies but in most forms, some patients will need admission to intensive care within days or weeks of onset

## Specific Antibodies and Syndromes

### NMDAR Antibody Encephalitis

NMDAR antibody-mediated encephalitis has become the most common form of autoimmune encephalopathy over the last few years. In a recent prospective study, up to 4% of patients with any cause of encephalitis (including infections) were found to have IgG antibodies against the GluN1 subunit of the NMDAR [15]. In the California Encephalitis project, the frequency of NMDAR antibody-mediated encephalitis seems to surpass any individual viral cause of encephalitis in young individuals [16]. NMDAR antibodies were initially described exclusively in young women with ovarian teratomas [10], but have now been described in patients between the age of 1 and 85, and ovarian teratomas are very rarely seen in children less than 12 years of age [17]. Other malignancies like testicular teratomas, Hodgkin's lymphoma, small cell lung carcinoma and neuroblastoma have been described in a few individual case reports often older patients and males.

A two stage disease process has been described [11, 18]. After a prodromal illness with fever and headache, most patients develop confusion or psychiatric symptoms (delirium, psychosis, catatonia) followed 10–20 days later by reduced consciousness, seizures, movement disorders, autonomic instability and respiratory depression. Various types of movement disorders have been identified which include orofacial dyskinesias (“rabbit mouth movements”), repetitive limb movements (e.g. choreoathetosis, cycling), waxy flexibility (catatonia), dystonia, chorea, opisthotonus, oculogyric crisis and even opsoclonus-myoclonus [19]. Isolated psychiatric presentations have been identified [10, 20] and prospective studies are currently underway to assess the antibody frequency in cohorts of psychosis patients. In children and males, seizures and movement disorders seem to be the more common presenting complaints [21, 22]. The CSF is usually cellular with lymphocytes, but oligoclonal bands are rare at onset. In some cases, white matter high signal has been seen and occasionally clinical and radiological demyelinating features similar to neuromyelitis optica spectrum disorders [23], particularly in children [24]. Given the prodromal symptoms, most patients are initially investigated for an infectious aetiology and in fact, several infections have been found concomitantly in these patients, including mycoplasma pneumoniae, HHV-6, enterovirus and herpes simplex virus (HSV) [18, 21, 25, 26]. In most cases, the significance of the other infections is unclear, but it is now recognised that patients, adults and children, can develop NMDAR antibodies after HSV encephalitis, when they relapse clinically with choreoathetosis, and with treatment, some have regained their post-HSV state [25, 27, 28].

The inference from experimental work is that reduction in NMDARs, particularly in those that control release from the inhibitory GABAergic neurons, causes an upregulation of extracellular glutamate resulting in a frontostriatal syndrome leading to the neuropsychiatric symptoms. At the same time, disinhibition of the brainstem central pattern regulators could be responsible for the hyperkinetic movements as well as the medullary-pontine network dysfunction that leads to central

hypoventilation [19, 29, 30]. However, although infusion of NMDAR antibodies into the ventricles of mice resulted in cognitive defects [31] or seizure susceptibility [32], neuropsychiatric symptoms, movement disorders or brainstem dysfunction have yet to be seen in mouse models of this form of encephalitis and the circuit defects in this highly complex disease remain unclear.

## **LGI1 Antibody Encephalitis**

Probably the most common form of the classical limbic encephalitis phenotype is associated with antibodies against LGI1. LGI1 is a secreted protein of the neuronal synapse, which interacts with pre-synaptic ADAM23 and post-synaptic ADAM22 proteins, and regulates the function of the VGKC subunits, Kv1.1 and Kv1.2 [33]. LGI1 mutations have been associated with autosomal dominant temporal lobe epilepsy. Patients with autoimmune limbic encephalitis are often middle-aged or elderly men (M:F 2:1), and present with memory impairment, confusion and seizures. Seizures often are in the form of facial grimacing and myoclonic jerks simultaneously affecting arm and occasionally leg on the same side; these have been described as faciobrachial dystonic or tonic seizures [34, 35]. The terminology of “seizures” has been disputed, as they are not often accompanied by electroencephalographic changes, but the patients have auras and post-epileptic automatisms which are consistent with epilepsy, even though the basal ganglia are clearly involved in the generation of the dystonic activity [36]. Other features of VGKC-complex/LGI1-Ab limbic encephalitis include rapid eye movement (REM) sleep disorder and rapidly progressive dementia. Tumours are uncommon but thymoma is occasionally seen. Nearly two-thirds of patients have serum hyponatremia at onset, which improves rapidly with fluid restriction and immunotherapies.

## **CASPR2 Antibody Encephalitis**

The other subtype of VGKC-complex antibody is variably associated with limbic encephalitis with sleep disturbance particularly insomnia, hallucinations, autonomic dysfunction and peripheral symptoms including neuromyotonia, neuropathic pain or cramp fasciculation syndrome. The combination of peripheral and central symptoms is called Morvan’s syndrome, which is more likely to be associated with thymomas, compared to those with pure CNS presentations [37]. Other presentations of CASPR2 antibodies include cerebellar ataxia [38], spinal myoclonic jerks and camptocormia [39]. CASPR2 is a transmembrane axonal protein of the neurexin IV superfamily found at the juxtaparanode of myelinated neurons in the peripheral and central nervous systems, and also at central synapses. Mutations in CASPR2 have been associated with rare forms of autism, obsessive compulsive disorder, schizophrenia, epilepsy and Tourette syndrome [40–43].

## **GABA<sub>B</sub>R Antibody Encephalitis**

GABA<sub>B</sub>R antibodies cause typical limbic encephalitis (memory loss, confusion, hallucinations and change in personality) with early and frequent seizures [44, 45]. Half of the patients have a paraneoplastic presentation, small cell lung cancer (SCLC) being the most common tumour. Paraneoplastic limbic encephalitis often precedes recognition of the tumour and is seen in older patients compared to the non-paraneoplastic ones. Prognosis is better than the paraneoplastic limbic encephalitis associated with anti-Hu antibodies and SCLC but there is seldom permanent improvement. Rarely cerebellar ataxia and opsoclonus-myoclonus have been described with GABA<sub>B</sub>R antibodies.

## **AMPA<sub>R</sub> Antibody Encephalitis**

Patients often present with subacute confusion, memory loss, confabulation or disorientation with associated psychiatric features and seizures. This antibody is usually seen in middle-aged women and is paraneoplastic in more than two-third of patients, with the tumour involving the thymus, lung or breast [7, 46, 47]. Symptoms usually respond well to immunotherapy but relapses are much more common than in the other syndromes, and may cause cumulative neurological deficits.

## **GABA<sub>A</sub>R Antibody Encephalitis**

This syndrome causes refractory seizures, status epilepticus, epilepsy partialis continua and rapidly progressive encephalopathy. This form of autoimmune encephalitis is less likely to be paraneoplastic (except occasional reports of thymoma) and responds very well to immunotherapy, although seizures may initially require pharmacologically induced coma [13]. Patients may have other less relevant concomitant antibodies against thyroid peroxidase, GAD or GABA<sub>B</sub>R. Seizures, memory impairment, hallucinations and anxiety were found to be the common manifestations and the clinical associations are less syndromic than previously thought [48].

## **Glycine Receptor Antibody-Mediated Syndrome**

Antibodies against the alpha-1 receptor of the glycine receptor (GlyR) have been identified in progressive encephalomyelitis rigidity and myoclonus (PERM) [12, 49]. The antibodies are likely to cause disruption of the inhibitory pathways of the brainstem and spinal cord. Typically, patients have oculomotor paresis, brainstem dysfunction, autonomic symptoms and encephalopathy. Brainstem dysfunction can be life-threatening associated with respiratory and occasionally cardiac disturbance. Similar to patients with mutations affecting the glycine receptor, exaggerated startle



response (hyperekplexia) is commonly seen. GlyR antibodies have also been found in patients with predominant stiff person syndrome, cerebellar ataxia, limbic encephalitis or optic neuritis [50, 51], but in these patients the relevance of the GlyR antibodies is less clear, and antibodies to GAD65 can be seen in a proportion of patients. 10% of patients can be paraneoplastic either due to a thymoma or lymphoma. Patients respond well to immunotherapy as with other neuronal surface antibody syndromes [51].

## **Glutamic Acid Decarboxylase (GAD) Antibody Related Syndromes**

Although patients with GAD antibodies may have stiff person syndrome (previously called spinal interneuronitis) causing muscle stiffness and exaggerated startle responses, these antibodies at equally high levels have also been seen in patients with cerebellar ataxia, limbic encephalitis or seizures. GAD antibodies can cause disinhibition of the GABAergic system causing continuous motor activity as demonstrated using an electromyogram (EMG) of the paraspinal and proximal muscles. As a result they suffer from muscle rigidity and spasms, which can be triggered by various sensory stimuli including loud noise, touch, change in ambient temperature or emotional upset (not dissimilar to hyperekplexia in PERM). Patients often require high doses of muscle relaxants like diazepam and baclofen, and some respond well to intravenous immunoglobulin (Jacob et al., unpublished data and [52, 53]). GAD antibodies are not usually paraneoplastic, but stiff person syndrome can occur in a paraneoplastic fashion when the antibody is targeted against a vesicular synaptic protein involved in endocytosis, called amphiphysin. The limbic encephalitis subtype due to GAD antibodies (predominant seizures) usually occurs in young women, is not paraneoplastic and shows a poor immunotherapy response.

---

## **Rarer Forms of Autoimmune Encephalitis**

### **DPPX Antibodies**

This was first described in a group of patients with prodromal gastrointestinal symptoms presenting with features of CNS hyperexcitability (aggression, hallucinations, tremors, myoclonus, seizures and hyperekplexia). Antibodies were identified against dipeptidyl-peptidase-like protein 6, DPPX which is a protein strongly associated with the Kv4.2 potassium channel [54]. The antibodies bind to the myenteric plexus, but the exact link with the diarrhoea is not clear. This is not usually a paraneoplastic phenomenon, but the severe diarrhoea may lead to weight loss and invoke suspicion of an underlying tumour. Patients often have very severe disease with lengthy hospital admissions and tend to relapse on tapering down the immunosuppression. The same antibodies curiously have been found in patients with a more PERM or SPS phenotype [55].

## **Metabotropic Glutamate Receptor (mGluR) Antibodies**

mGluR antibodies are usually linked with Hodgkin's lymphoma either causing cerebellar ataxia (mGluR1) [56] or limbic encephalitis (mGluR5, Ophelia syndrome) [57, 58]. The antibodies are highly expressed in the cerebellum and hippocampus, respectively. Patients often have a complete recovery after the treatment of lymphoma or immunotherapy, but this syndrome has been described in only a handful of patients.

## **Dopamine 2 Receptor (D2R) Antibodies**

A basal ganglia encephalitis causing various movement disorders like dystonia, chorea, tremor, oculogyric crisis and parkinsonism was initially described in a paediatric population, who also frequently had agitation, anxiety, psychosis and insomnia [59]. Response to immunotherapy is often partial with residual deficits in motor, cognitive and psychiatric function. However the frequency of antibodies in similar patients is very low in subsequent studies [50], and it is not clear if they are present in adults.

## **IgLON5 Antibodies**

As opposed to the other acute/subacute encephalitic syndromes described so far, IgG4 antibodies against immunoglobulin-like domain-containing protein (IgLON-5, a neuronal cell adhesion molecule) cause a more prolonged onset (mean 5 years) non-REM and REM parasomnia with sleep disordered breathing and later developing dysarthria, dysphagia, chorea and ataxia. Symptoms in the few cases reported so far do not respond to immunotherapy and post-mortem studies demonstrate a tauopathy [60]. Further studies are needed to understand the exact role of antibodies and its possible link to neurodegeneration.

## **Bickerstaff's Brainstem Encephalitis**

This is a brainstem encephalitic syndrome which overlaps with Guillain-Barré syndrome (GBS). Patients often present with subacute (less than 4 weeks) onset of altered consciousness, ataxia and ophthalmoplegia [61, 62]. Hyporeflexic paralysis resembling GBS may be seen, but because of brainstem involvement the reflexes can also be brisk. Patients have brainstem features including facial palsy, pupillary changes, bulbar palsy and upper motor neuron signs. This is frequently a post-infectious monophasic inflammatory condition and more than 70% patients have antibodies against GQ1b, a ganglioside. Most patients improve within 12 weeks of onset of the illness. In children, not only GQ1b antibodies, but some of the patients have another neuronal antibody (NMDAR, GlyR, MOG or aquaporin-4 antibodies) which may contribute to additional clinical features [63].

## Hashimoto's Encephalopathy

This is a form of encephalitis which by definition should be associated with thyroid antibodies and a substantial clinical response to steroids. However, the literature includes many cases that could be better described within the categories above [64], and a proportion of which have NMDAR or VGKC-complex antibodies. Thus Hashimoto's encephalitis should probably be restricted to those patients in whom no other antibody can be identified and who have a surprisingly rapid response to steroids. Indeed, it has been renamed as steroid responsive encephalopathy associated with autoimmune thyroiditis [65]. Patients are usually women (age range, 10–70) and often present with subacute encephalopathy, with seizures, myoclonus, hallucinations (usually visual) and stroke-like episodes. Patients have positive anti-thyroid (thyroid peroxidase or thyroglobulin) antibodies and may have clinical or sub-clinical hypothyroidism (although some have normal thyroid function). Brain MRI can be normal, and the neuronal surface antibodies should be absent as mentioned above. Transient multifocal T2-weighted and fluid attenuation inversion recovery (FLAIR) hyperintensities in the subcortical regions/brainstem and cerebellar atrophy have occasionally been described [66]. As the name implies patients respond to steroids or in steroid-resistant patients, IVIg [67].

## Susac's Syndrome

A triad of encephalopathy, branched retinal artery occlusions and sensorineural hearing loss defines this autoimmune vasculopathy causing microinfarcts in the brain, retina or inner ear. MRI changes predominantly involve the corpus callosum with punched out or snow-ball like appearance [68, 69]. Patients may not always have all the three components (only in 13% in a comprehensive review, [68]) and can have variable response to immunotherapy. Other terms used to describe this condition include retinocochleocerebral vasculopathy, RED-M (retinopathy, encephalopathy, deafness associated microangiopathy) and SICRET (small infarcts of cochlear, retinal and encephalic tissues) [69].

---

## Diagnosis

The diagnosis in this expanding group of diseases is made with a high index of clinical suspicion as outlined in the clinical details of individual syndromes above. Recently diagnostic guidelines have been proposed for presumed autoimmune encephalitis (Table 2.2) and NMDAR antibody encephalitis (Table 2.3) [70]. In the NMDAR antibody patients, the CSF examination is often pleocytotic (80%), with elevated protein (30%) and positive oligoclonal bands (50%), but this may not always be florid. In limbic encephalitis, the CSF varies depending partly on the type of antibody with often normal findings in patients with LGI1 antibodies.

**Table 2.2** Diagnostic criteria for possible autoimmune encephalitis

*All the following three criteria need to be met to make a diagnosis of possible autoimmune encephalitis:*

1. Subacute (less than 3 months) onset of short term memory loss, altered level of consciousness, lethargy, personality change or psychiatric symptoms
2. At least one of the following:
  - (a) Seizures—not explained by a previously diagnosed seizure disorder
  - (b) Focal central nervous system signs
  - (c) CSF white cell count more than  $5/\text{mm}^3$
  - (d) MRI showing T2W/FLAIR high signals in medial temporal lobes or multifocal demyelination/inflammatory changes in grey or white matter
3. Reasonable exclusion of other causes (e.g. infective, metabolic, toxic, CJD, neoplastic, rheumatological and mitochondrial disorders)

Adapted from [70]

**Table 2.3** Diagnostic criteria for anti-NMDAR encephalitis

*Major group symptoms*

Subacute (less than 3 months) onset of:

1. Abnormal psychiatric behaviour or cognitive dysfunction
2. Speech dysfunction (pressured speech, verbal reduction, mutism)
3. Seizures
4. Movement disorders, dyskinesias, rigidity or abnormal postures
5. Decreased level of consciousness
6. Autonomic dysfunction or central hypoventilation

*Laboratory abnormalities:*

1. Abnormal EEG—focal or diffuse slowing, disorganised activity, extreme delta brush or epileptiform changes
2. CSF with pleocytosis or oligoclonal bands
3. Presence of a specific neuronal or glial antibody

*Probable anti-NMDAR encephalitis—all three need to be satisfied:*

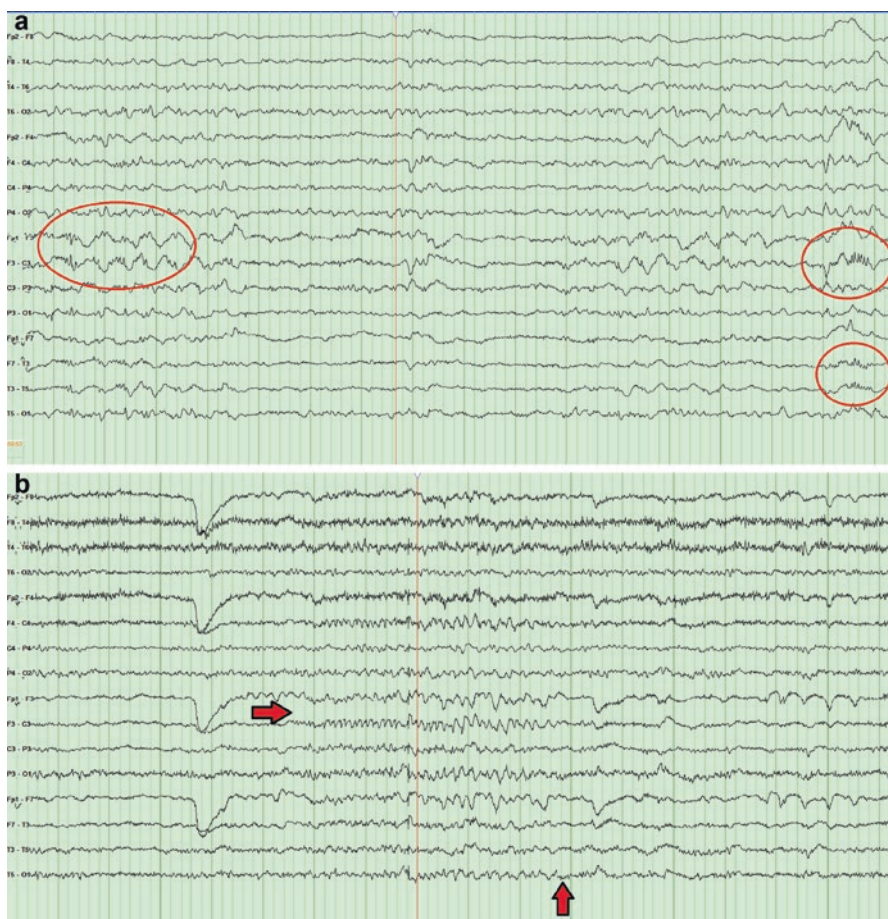
- A. 4 out of 6 major group symptoms
- B. At least one of the two laboratory abnormalities
- C. Reasonable exclusion of other disorders

*Definite anti-NMDAR encephalitis—all three need to be satisfied:*

- A. 1 out of the 6 major group symptoms
- B. Presence of IgG NMDAR antibodies
- C. Reasonable exclusion of other disorders

Adapted from [70]

EEG demonstrates non-specific slowing in the majority of autoimmune encephalitides. NMDAR antibody encephalitis can show a very specific EEG pattern of “extreme delta brush” seen in up to a third of patients, especially when they are severely affected. This is characterised by rhythmic delta waves (1–3 Hz) with superimposed bursts of beta waves (20–30 Hz), resembling the delta brush pattern seen in premature infants. Unlike the premature infant EEG pattern, however, the extreme delta brush pattern seen in this form of encephalitis tends to be symmetric and synchronous and occurs continuously without any change with the sleep-wake cycle, stimulation/arousal levels or the involuntary movements.



**Fig. 2.2** EEG changes in NMDAR encephalitis. Panel (a) showing extreme delta brushes over the left cerebral hemisphere. Panel (b) depicts brief ictal rhythmic discharges (BIRDS) with abrupt onset of paroxysmal rhythmic activity that evolves in frequency and amplitude. Note however that this also ends abruptly in (Horizontal arrow onset; vertical arrow offset) and therefore does not fit the standard definition of an electrographic seizure, traditionally required to last a minimum of 10 s (originally published in [71])

Brief ictal rhythmic discharges (BIRDS) which involve abrupt onset and termination of rhythmic discharges are occasionally seen (Fig. 2.2) [71].

MRI can be very useful and show high signal changes on T2-weighted or FLAIR sequences across the medial temporal lobe, without any contrast enhancement, especially in NMDAR and GABABR antibody patients. Occasionally signal changes have been described in the frontal and parietal cortex, which may sometimes be associated with hypermetabolism on (18F)-fluorodeoxyglucose positron emission tomography (FDG-PET) scans in the acute stages. LGI1, GABABR and AMPAR antibody patients typically have medial temporal lobe hyperintensities on FLAIR

but sometimes have normal scans. Anti-GABA<sub>A</sub>R encephalitis often causes extensive/multifocal T2W/FLAIR high signal changes in the cortical and subcortical regions. Hashimoto's encephalopathy patients often have normal scans, but can occasionally have abnormal signal changes as mentioned above.

All patients with autoimmune encephalitis should undergo a comprehensive screening to detect any underlying neoplasia. Initial screening is often done with a CT scan (chest, abdomen and pelvis) with contrast, and in patients with NMDAR antibody encephalitis, additional ovarian or testicular ultrasound is essential. If this is normal, our practice is to do a whole body PET scan. Rescanning in a few months is often useful when the patients do not respond to standard immunotherapies or relapse after initial improvement. LGI1 antibodies are less likely to be paraneoplastic compared to GABA<sub>B</sub>R or AMPAR antibodies.

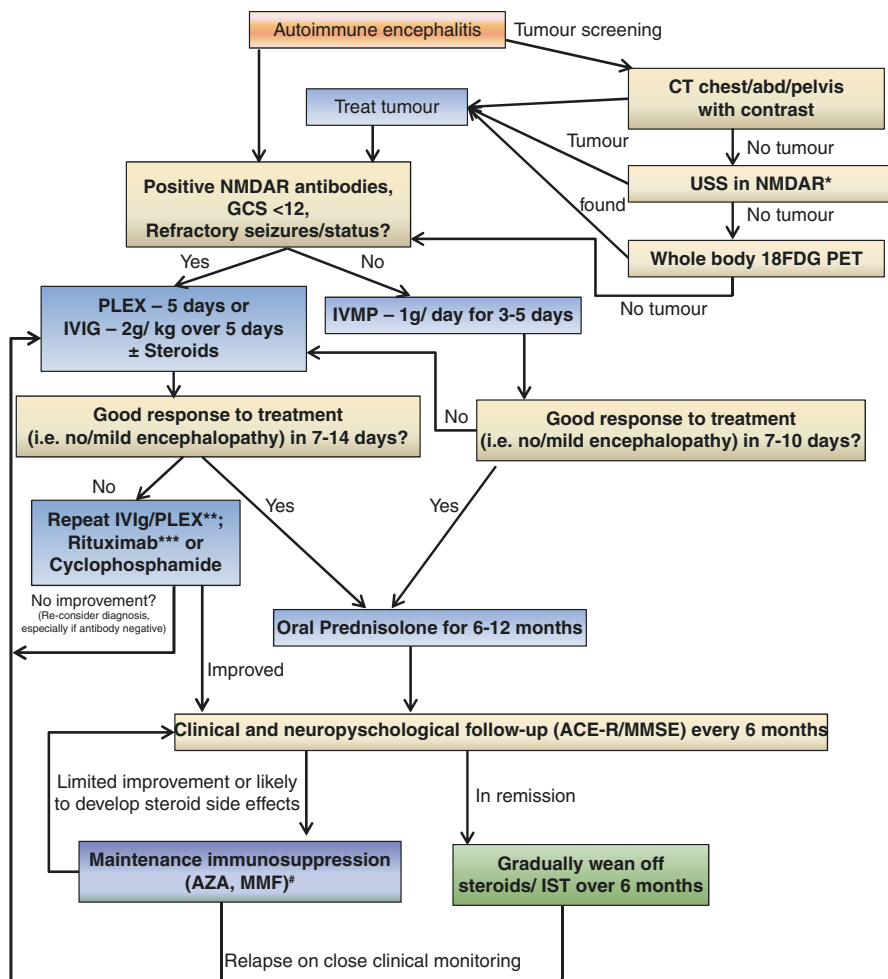
---

## Antibody Testing

The laboratory evaluation of all forms of autoimmune encephalitides involves an indirect and direct approach. Initial evaluation may be done using indirect immunofluorescence using rat/primate brain sections; this can demonstrate striking antibody binding to the neuropil of the hippocampus but does not easily discriminate between different antigens. Use of cell based assays on human embryonic kidney (HEK) cells transfected with DNA to express the appropriate membrane antigen is a more sensitive and specific technique and, if live cells are used, this demonstrates the binding to extracellular epitopes of the neuronal surface antigen. CSF examination for antibodies should be performed if possible, especially if the initial assay using serum is negative. Even though the absolute antibody concentration is almost always higher in the serum, it is possible that serum antibodies are occasionally missed; this is because serum is always tested diluted (1:20, 1:50 or 1:100), whereas CSF is often tested undiluted or 1:1.

Live cell assays have been shown to be slightly more sensitive and they should only detect pathogenic antibodies that can bind to extracellular antigen domains, but they are time consuming and costly because of the tissue culture involved. Moreover, they can detect low levels of antibodies (e.g. NMDAR) in a small proportion (<3%) of patients with inflammatory disease that may not always be clinically relevant. Most diagnostic assays are performed with commercially available fixed cells provided on glass slides. In experienced laboratories the commercial assay has been shown to be equally effective in picking up the antibodies and has the advantage of a very quick turnaround time. However, given that the cells are permeabilised and fixed, they can be difficult to interpret due to non-specific intracellular binding, and they may be less sensitive, unless interpreted by experienced personnel.





**Fig. 2.3** Treatment algorithm for autoimmune encephalitis (refer Abbreviations). \*Transvaginal ultrasound preferred in females and testicular ultrasound in men. \*\*It is recommended that IVIg is not followed soon after (within 2–3 weeks) by Plex to avoid the previous IVIg dose to be washed out. A further course of IVIg may be preferable in these circumstances, if second line treatment cannot be given. \*\*\*Second line treatments—Rituximab is either given as 375 mg/m<sup>2</sup> every week for four cycles or 1 g every fortnight for two cycles; cyclophosphamide is best given as per local protocols for vasculitis, with appropriate corrections for age and renal function (e.g. 15 mg/kg IV pulse every 2–3 weeks for 6 cycles, if patients less than 60 years and normal renal function). #There are no randomised controlled trials for maintenance immunosuppression in autoimmune encephalitis. Mycophenolate seems to be better tolerated and less likely to cause relapses from limited literature evidence and personal experience

## Treatment

There are no randomised controlled trials in patients with autoimmune encephalitis

and the treatment recommendation comes from various case series and cohort studies. After controlling the acute episode with a combination of immunosuppressants (see below) and other symptomatic therapies (e.g. anti-epileptics, anti-psychotics, neuropathic analgesics, etc.) most patients will receive maintenance immunosuppression which may be tapered off after a few months but might be required for years depending on the response. A commonly used algorithmic approach is outlined (Fig. 2.3).

Most patients are given a combination of first line (intravenous immunoglobulin (IVIg), steroids or plasma exchange (PLEX)), followed by second line (rituximab or cyclophosphamide) immunotherapy if the response is slow [17, 72]. There is anecdotal evidence that patients receiving rituximab tend to have less number of relapses and possibly a better long-term outcome and some centres are recommending its use early in the disease, though in many countries this is restrained by the cost. Our recommendation is to tailor the treatment based on the clinical severity. For example, if a patient is in status epilepticus or is severely comatose, it might be best to undertake PLEX first, so that IVIg can be used as a second line agent. This is especially true if both PLEX and IVIg are contemplated at the outset, to avoid any IVIg being washed out by a consequent PLEX. In patients with VGKC-complex (LGII, CASPR2) encephalitis, intravenous methyl prednisolone followed by oral prednisolone seems to be sufficient as the first line treatment. Addition of IVIg or PLEX to steroids was not shown in the initial studies to alter the 4-year outcome of the LGII/CASPR2 patients, although these were retrospective analyses [6].

Most commonly used anti-epileptics include levetiracetam and carbamazepine, and many patients with NMDAR antibody-mediated encephalitis would benefit from olanzapine, when they have prominent psychiatric symptoms. Refractory seizures in GABA<sub>A</sub>R antibody-mediated encephalitis may require ventilation and pharmacologically induced coma [13].

Once the acute episode is controlled, patients (especially NMDAR) require maintenance oral Prednisolone (usually for 6–12 months), and most experts do not automatically add a steroid sparing drug like Azathioprine or Mycophenolate (MMF), unless there are relapses. No data exists to compare the efficacy between the drugs, but in neuromyelitis optica (NMO) there are some anecdotal reports to suggest that azathioprine tends to have higher annualised relapse rate compared to MMF or rituximab [73, 74]. Many NMO patients also tend to discontinue azathioprine because of tolerability [75]. This is yet to be shown in the context of autoimmune encephalitis.

Patients with an underlying tumour should have the tumour removed and studies have shown that this subgroup of patients tends to do better in the long term than those with purely autoimmune forms, at least with NMDAR antibodies [17, 76].

---

## Prognosis

In NMDAR antibody encephalitis, early treatment, lack of need for intensive care admission, modified Rankin scale of  $\leq 3$  and use of second line immunosuppressants were associated with better long-term outcome [17], but irrespective of



treatments some patients (12–20%) relapsed (usually within the first 2 years of diagnosis) after initial response to immunosuppression. The relapse is usually a limited form of the initial syndrome and also responds to immunotherapy. LGI1 antibody-mediated encephalitis patients often have a monophasic illness (some patients can go into spontaneous remission) with rapid response to immunomodulation and relapses are less common. However, the LGI1 patients can have a more protracted course before the diagnosis is made, and hence are more likely to have persistent neurocognitive symptoms in the form of executive dysfunction, memory impairment and anxiety, which have been less commonly reported in the more aggressive onset NMDAR encephalitis. Treatment response is best assessed by clinical symptoms rather than antibody titres. CSF levels may be more helpful but as comparisons should always be made with previous titres this is impractical unless suitable previous CSF samples are available. Although serum levels may not reflect so well with the clinical symptoms, they can help in assessing whether the immunotherapies are effective in reducing the levels. In general, most patients respond exceedingly well to immunotherapy (and tumour removal, if applicable) especially if instituted early in the disease course, but long-term memory or psychiatric sequelae are beginning to be recognised in all forms of autoimmune encephalitis.

---

## Conclusion

Autoimmune encephalitis and related syndromes secondary to neuronal cell surface have emerged over the last decade with new antibodies being identified. The prompt identification of this group of conditions is crucial since the patients can have a nearly completely reversible syndrome, especially when diagnosed and treated early. It is still unclear how the antibody response is initiated, or how this immune response is propagated to the central nervous system. Future translational research may give insights into novel diagnostic and therapeutic approaches in this rapidly expanding field of neuroimmunology.

---

## References

1. Brierley J, Corsellis J, Hierons R, Nevin S. Subacute encephalitis of later adult life. Mainly affecting the Limbic areas. *Brain*. 1960;83:357–68.
2. Brain WR, Daniel PM, Greenfield JG. Subacute cortical cerebellar degeneration and its relation to carcinoma. *J Neurol Neurosurg Psychiatry*. 1951;14(2):59–75.
3. Graus F, Cordon-Cardo C, Posner JB. Neuronal antinuclear antibody in sensory neuronopathy from lung cancer. *Neurology*. 1985;35(4):538–43.
4. Moscato EH, Jain A, Peng X, Hughes EG, Dalmau J, Balice-Gordon RJ. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. *Eur J Neurosci*. 2010;32(2):298–309.
5. Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol*. 2001;50(1):73–8.

6. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010;133(9):2734–48.
7. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009;65(4):424–34.
8. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol*. 2010;9(1):67–76.
9. Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain*. 2005;128(Pt 8):1764–77.
10. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61(1):25–36.
11. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain*. 2010;133(Pt 6):1655–67.
12. Hutchinson M, Waters P, McHugh J, Gorman G, O'Riordan S, Connolly S, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology*. 2008;71(16):1291–2.
13. Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014;13(3):276–86.
14. Irani SR, Lehmann-Horn K, Geschwind M, Wang S, Vincent A, von Budingen HC. The active intrathecal B-cell response in LGI1-antibody encephalitis. *Lancet*. 2015;385(Suppl 1):S46.
15. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10(12):835–44.
16. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis*. 2012;54(7):899–904.
17. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157–65.
18. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091–8.
19. Kleinig TJ, Thompson PD, Matar W, Duggins A, Kimber TE, Morris JG, et al. The distinctive movement disorder of ovarian teratoma-associated encephalitis. *Mov Disord*. 2008;23(9):1256–61.
20. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol*. 2011;258(4):686–8.
21. Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr*. 2013;162(4):850–6.e2.
22. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol*. 2009;66(1):11–8.
23. Titulaer MJ, Hofberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;75(3):411–28.

24. Hachohen Y, Zuberi S, Vincent A, Crow YJ, Cordeiro N. Neuromyelitis optica in a child with Aicardi-Goutieres syndrome. *Neurology*. 2015;85(4):381–3.
25. Armangue T, Leypoldt F, Malaga I, Raspall-Chaure M, Marti I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol*. 2013;75(2):317–23.
26. Pruss H, Finke C, Holtje M, Hofmann J, Klingbeil C, Probst C, et al. *N*-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol*. 2012;72(6):902–11.
27. Hachohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, et al. *N*-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord*. 2014;29(1):90–6.
28. Titulaer MJ, Leypoldt F, Dalmau J. Antibodies to *N*-methyl-D-aspartate and other synaptic receptors in choreoathetosis and relapsing symptoms post-herpes virus encephalitis. *Mov Disord*. 2014;29(1):3–6.
29. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. *Neurology*. 2011;77(2):179–89.
30. Tuzun E, Zhou L, Baehring JM, Bannayk S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol*. 2009;118(6):737–43.
31. Planaguma J, Leypoldt F, Mannara F, Gutierrez-Cuesta J, Martin-Garcia E, Aguilar E, et al. Human *N*-methyl-D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain*. 2015;138(Pt 1):94–109.
32. Wright S, Hashemi K, Stasiak L, Bartram J, Lang B, Vincent A, et al. Epileptogenic effects of NMDAR antibodies in a passive transfer mouse model. *Brain*. 2015;138(Pt 11):3159–67.
33. Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol*. 2012;8(7):380–90.
34. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol*. 2011;69(5):892–900.
35. Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? *Neurology*. 2011;76(15):1355–7.
36. Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schneider SA, Pettingill P, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain*. 2013;136(Pt 10):3151–62.
37. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol*. 2012;72(2):241–55.
38. Becker EB, Zuliani L, Pettingill R, Lang B, Waters P, Dulneva A, et al. Contactin-associated protein-2 antibodies in non-paraneoplastic cerebellar ataxia. *J Neurol Neurosurg Psychiatry*. 2012;83(4):437–40.
39. Sadalage G, Yousaf MA, Karim AR, Jacob S. Keep your head down and shake.
40. Gregor A, Albrecht B, Bader I, Bijlsma EK, Ekici AB, Engels H, et al. Expanding the clinical spectrum associated with defects in CNTNAP2 and NRXN1. *BMC Med Genet*. 2011;12:106.
41. Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med*. 2006;354(13):1370–7.
42. Verkerk AJ, Mathews CA, Joosse M, Eussen BH, Heutink P, Oostra BA. CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics*. 2003;82(1):1–9.
43. Rodenas-Cuadrado P, Pietrafusa N, Francavilla T, La Neve A, Striano P, Vernes SC. Characterisation of CASPR2 deficiency disorder—a syndrome involving autism, epilepsy and language impairment. *BMC Med Genet*. 2016;17:8.
44. Hoftberger R, Titulaer MJ, Sabater L, Dome B, Rozsas A, Hegedus B, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology*. 2015;81(17):1500–6.
45. Jeffery OJ, Lennon VA, Pittock SJ, Gregory JK, Britton JW, McKeon A. GABAB receptor autoantibody frequency in service serologic evaluation. *Neurology*. 2013;81(10):882–7.

46. Bataller L, Galiano R, Garcia-Escrig M, Martinez B, Sevilla T, Blasco R, et al. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. *Neurology*. 2010;74(3):265–7.
47. Graus F, Boronat A, Xifro X, Boix M, Svigelj V, Garcia A, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. *Neurology*. 2010;74(10):857–9.
48. Pettingill P, Kramer HB, Coebergh JA, Pettingill R, Maxwell S, Nibber A, et al. Antibodies to GABAA receptor alpha1 and gamma2 subunits: clinical and serologic characterization. *Neurology*. 2015;84(12):1233–41.
49. Mas N, Saiz A, Leite MI, Waters P, Baron M, Castano D, et al. Antiglycine-receptor encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry*. 2011;82(12):1399–401.
50. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann N Y Acad Sci*. 2015;1338:94–114.
51. Carvajal-Gonzalez A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain*. 2014;137(Pt 8):2178–92.
52. Dalakas MC. The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. *J Neurol*. 2005;252(Suppl 1):119–25.
53. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med*. 2001;345(26):1870–6.
54. Boronat A, Gelfand JM, Gresa-Arribas N, Jeong HY, Walsh M, Roberts K, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol*. 2013;73(1):120–8.
55. Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. *Neurology*. 2014;83(20):1797–803.
56. Marignier R, Chenevier F, Rogemond V, Sillevs Smitt P, Renoux C, Cavillon G, et al. Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? *Arch Neurol*. 2010;67(5):627–30.
57. Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulos M, Weaver S, Antoine JC, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology*. 2011;77(18):1698–701.
58. Mat A, Adler H, Merwick A, Chadwick G, Gullo G, Dalmau JO, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. *Neurology*. 2013;80(14):1349–50.
59. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain*. 2012;135(Pt 11):3453–68.
60. Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol*. 2014;13(6):575–86.
61. Koga M, Kusunoki S, Kaida K, Uehara R, Nakamura Y, Kohriyama T, et al. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. *J Neurol Neurosurg Psychiatry*. 2012;83(12):1210–5.
62. Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome. *Brain*. 2003;126(Pt 10):2279–90.
63. Hacohen Y, Nishimoto Y, Fukami Y, Lang B, Waters P, Lim MJ, et al. Paediatric brainstem encephalitis associated with glial and neuronal autoantibodies. *Dev Med Child Neurol*. 2016;58:836–41.
64. Tuzun E, Erdag E, Durmus H, Brenner T, Turkoglu R, Kurtuncu M, et al. Autoantibodies to neuronal surface antigens in thyroid antibody-positive and -negative limbic encephalitis. *Neurol India*. 2011;59(1):47–50.

65. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol*. 2006;63(2):197–202.
66. Song YM, Seo DW, Chang GY. MR findings in Hashimoto encephalopathy. *AJNR Am J Neuroradiol*. 2004;25(5):807–8.
67. Jacob S, Rajabally YA. Hashimoto's encephalopathy: steroid resistance and response to intravenous immunoglobulins. *J Neurol Neurosurg Psychiatry*. 2005;76(3):455–6.
68. Dorr J, Krautwald S, Wildemann B, Jarius S, Ringelstein M, Duning T, et al. Characteristics of Susac syndrome: a review of all reported cases. *Nat Rev Neurol*. 2013;9(6):307–16.
69. King D, Appleton JP, Jacob S. Susac's syndrome: a case series from a regional neuroscience unit. *J Neurol Neurosurg Psychiatry*. 2015;86(11):e4. <https://doi.org/10.1136/jnnp-2015-312379.129>.
70. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15:391–404.
71. Abbas A, Garg A, Jain R, Mazibrada G, Jacob S. Extreme delta brushes and BIRDS in the EEG of anti-NMDA-receptor encephalitis. *Pract Neurol*. 2016;16:326–7.
72. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10(1):63–74.
73. Jeong IH, Park B, Kim SH, Hyun JW, Joo J, Kim HJ. Comparative analysis of treatment outcomes in patients with neuromyelitis optica spectrum disorder using multifaceted endpoints. *Mult Scler*. 2016;22(3):329–39.
74. Mealy MA, Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. *JAMA Neurol*. 2014;71(3):324–30.
75. Elson L, Kitley J, Luppe S, Lythgoe D, Mutch K, Jacob S, et al. Long-term efficacy, tolerability and retention rate of azathioprine in 103 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder patients: a multicentre retrospective observational study from the UK. *Mult Scler*. 2014;20(11):1533–40.
76. Tanyi JL, Marsh EB, Dalmau J, Chu CS. Reversible paraneoplastic encephalitis in three patients with ovarian neoplasms. *Acta Obstet Gynecol Scand*. 2012;91(5):630–4.

# Acute Demyelinating Emergencies

# 3

Jean-Christophe Ouallet

---

## Introduction

Acute demyelinating emergencies usually refer to acute idiopathic inflammatory diseases with white matter involvement of the central nervous system (CNS). Inflammatory demyelinating diseases of the CNS occur worldwide and are the leading cause of non-traumatic neurological disability in young adults.

Acute demyelinating disease may refer to one of the several conditions, viz., severe clinically isolated syndrome (CIS) at high risk for multiple sclerosis (MS), clinically definite MS or tumefactive variants of MS (tumefactive demyelinating lesion (TDL) [1], Balo, Marburg), acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO or Devic disease) or other idiopathic acute inflammatory attacks of the CNS of unknown (mostly autoimmune) origin with various overlapping syndromes [2]. Occasionally, acute demyelinating conditions may also refer to secondary acute inflammatory events of diverse origin, such as infectious or post-infectious, autoimmune (systemic lupus erythematosus [SLE] and others), paraneoplastic and granulomatosis (such as sarcoidosis).

---

## Epidemiology [3]

Acute demyelinating emergencies involving the CNS usually affect young adults or children. Non-Caucasian patients are susceptible to more severe acute demyelinating events of the CNS than Caucasians. On the other hand, demyelinating diseases, notably MS, are more common in Caucasians, being more frequent in Northern Europe and North America compared with other parts of the world.

---

J.-C. Ouallet (✉)

Department of Neurology, Multiple Sclerosis Center, University of Bordeaux, Hôpital Pellegrin-Tripode, Bordeaux Cedex, France

e-mail: [jean-christophe.ouallet@chu-bordeaux.fr](mailto:jean-christophe.ouallet@chu-bordeaux.fr)

Although MS is believed to be less prevalent in Oriental people and those from the Arabian Peninsula, Africa, continental South America and India, severe acute atypical demyelinating forms of the disease occur more frequently in these populations.

## Clinical Features

The clinical presentation generally reveals a rapidly evolving, progressive focal impairment of the CNS that is typically suggestive of an inflammatory mechanism [4].

The following features may be suggestive of this group of diseases:

- Progression of neurological deficits over hours, days or weeks. The progression to a nadir between 4 h and 21 days after onset of symptoms has been proposed by the Transverse Myelitis Consortium Working Group [5].
- Presence of deficits in the central motor, sensory, cerebellar, brain stem or optic nerve. Typical and non-typical neurological signs of MS have been reported by an international expert task force [6]. The main clinical features of acute demyelinating events are summarized in Table 3.1.
- Absence of other conditions (differential diagnosis):
  - acute impairment (starting in seconds) suggestive of stroke or epilepsy,
  - diffuse non-focal impairment suggestive of myasthenia gravis or Guillain–Barré syndrome with loss of peripheral reflexes and
  - slow progressive impairments, which are more suggestive of a tumoural origin (worsening in months) or a degenerative origin (worsening in years). In the case of a medullary syndrome, magnetic resonance imaging (MRI) is warranted urgently to exclude a medullary compression.

**Table 3.1** Main clinical features of acute demyelinating events

Typical	Do not forget to check for
Fast progression in hours, days or weeks (typically between 4 h and 21 days) Partial or transverse myelitis Optic neuritis Nystagmus, complex ophthalmoplegia Cerebellar signs	Accurate medical history Thoracic hypoaesthesia, cutaneous reflexes, pallesthesia, urinary retention or urgency Visual acuity and fields, Marcus Gunn sign Oculomotricity Tandem (straight line) walking, coordination
<i>Less typical but possible in severe acute demyelinating emergencies</i>	
Fever, headache, confusion, loss of vigilance Aphasia, apraxia, agnosia and encephalitic syndrome Neurovegetative symptoms: nausea	Acute disseminated encephalomyelitis Cognitive functions

- An investigation for past neurological episodes and signs of systemic autoimmunity is mandatory (mouth and eye dryness [Sicca syndrome], arthralgia, skin, renal or lung involvement).
- An investigation for present or past systemic infectious or toxic determinants is also mandatory.

Table 3.2 summarizes the main autoimmune aetiologies; Table 3.3 shows the main infectious aetiologies that should orient the clinical and paraclinical investigations. In Table 3.4, the most important diseases, in terms of a differential diagnosis, are summarized.

## Investigations

### Immediate Paraclinical Investigations

*MRIs of the brain and spinal cord* are the main investigations to be performed immediately. MRI is especially important to exclude other immediate and serious diagnoses,

**Table 3.2** Main autoimmune causes of acute severe demyelinating diseases of the central nervous system

Diagnosis	Frequency/characteristics
Clinically isolated syndrome or acute idiopathic inflammatory attack	Frequent (probably the most frequent)
Acute disseminated encephalomyelitis and post-infectious demyelination	Frequent ( <i>see</i> Tables 3.3 and 3.5)
Multiple sclerosis	Frequent, usually less severe
Neuromyelitis optica (NMO)	Frequent, check for serum anti-NMO/AQP4 IgG and anti-MOG IgG
Idiopathic acute transverse myelitis	Frequent
Gougerot–Sjögren syndrome	Rare (chronic but also acute)
Systemic lupus erythematosus	Rare, antinuclear antibody (ANA) testing
Sarcoidosis	Rare (chronic or subacute rather than acute)
Anti-phospholipid syndrome	Rare (strokes rather than acute demyelinating)
Behçet syndrome	Rare (oral and genital recurrent ulcerations)
Paraneoplastic demyelination (anti-NMDAr, VGKC, Ma <sub>2</sub> )	Rare (usually less acute). Test antibodies in serum and CSF
Hashimoto anti-TPO encephalitis, anti-GQ1B	Rare
Bickerstaff encephalitis, anti-GAD encephalitis	Rare: Acute onset or worsening of the chronic disease, sometimes after infectious or traumatic injury
Leucodystrophy: CASH syndrome, adrenoleucodystrophy	Exceptional
Cerebral vasculitis	Exceptional
Systemic sclerosis	Exceptional
Wegener, Churg–Strauss, Cogan, Susac, Sharp syndromes	Exceptional
Coeliac disease	Exceptional, seizures and cerebellar symptoms
Other	Rare



**Table 3.3** Main infectious agents involved in the aetiology or differential diagnosis of acute demyelinating diseases of the central nervous system

Virus	<i>Not very frequent:</i> Herpes virus ( <i>HSV1 and HSV2, VZV + + +</i> , CMV, EBV, HHV6 A), enterovirus (echovirus, poliovirus, coxsackie A and B), HIV, JC virus (PML). <i>Rare:</i> Hepatitis A, hepatitis B, hepatitis C, adenovirus, rubella, lymphocytic choriomeningitis virus, rabies, arbovirus (dengue), paramyxovirus (measles, mumps, respiratory syncytial virus), myxovirus influenzae, West Nile, Japanese encephalitis virus, St Louis encephalitis virus, tick-borne meningoencephalitis
Bacteria	<i>Not very frequent:</i> Lyme/ <i>Borrelia</i> , mycobacterial infection (tuberculosis or atypical)., <i>Rare:</i> <i>Listeria</i> , <i>Brucella</i> , <i>mycoplasma</i> , <i>rickettsia</i> , Whipple. <i>Exceptional:</i> <i>Leptospira</i> , pertussis, <i>Coxiella burnetii</i> , <i>Nocardia</i> , <i>chlamydia</i> , <i>Treponema pallidum</i>
Parasites	<i>Rare:</i> <i>Echinococcus bilharziose</i> , hydatid, <i>Toxoplasma</i> , <i>Trichinella</i> , <i>Toxocara</i> , cysticercosis, <i>Strongyloides</i> , <i>Gnathostoma</i> , <i>Plasmodium falciparum</i> , distomatose, loa-loa, <i>Taenia</i> , <i>Schistosoma</i> , anguillule
Mycoses	<i>Rare:</i> Blastomycosis, coccidioidomycosis, actinomycosis, cryptococcosis, aspergillosis, candidiasis, histoplasmosis

**Table 3.4** Main differential diagnoses of acute demyelinating diseases of the central nervous system

Diagnosis	Main features
Spinal cord compression	Spinal cord MRI+++
Guillain-Barré syndrome	Symmetrical loss of reflexes
Lymphoma	MRI: Intense post-contrast enhancement, diffusion restriction,
Glioma	Lipid peak on spectroscopy, not acute, mass effect
Infectious agents ( <i>see Table 3.3</i> )	Fever, meningitis
Toxic: Anoxia, oxygen (high delivery), CO, NO, Cu, heroin	Encephalopathy, extensive bilaterally symmetrical signal hyperintensity on MRI
Post-radiation	Usually normal CSF
Metabolic, Leigh syndrome, RANBP2 related encephalopathy, biotin-responsive basal ganglia disease	Encephalopathy, check for ammonaemia, vitamin B <sub>12</sub> , homocysteinaemia, lactate/pyruvate, vitamin B <sub>1</sub> /centropontine myelinolysis, coenzyme Q10, RANBP2 genetic testing, biotinidase, biotin therapeutic test
Ischaemic or haemodynamic	Angiography, diffusion MRI, blood pressure, headache, eclampsia, vasoconstrictive drugs
Post-seizure	Recent prolonged seizure/status epilepticus

such as those of a vascular or compressive origin (i.e. spinal cord compression). Computed tomography (CT) is usually of little use, other than ruling out haemorrhage.

*Blood tests* that are performed routinely to exclude a CNS disease associated with systemic infection or inflammation and other systemic disturbances include a haemogram, biochemistry, erythrocyte sedimentation rate, C-reactive protein (CRP), immunoglobulin analysis and coagulation parameters.

## Other Paraclinical Tests [4, 7]

It is mandatory to complete various investigations, depending on the clinical presentation and the results from the MRI. The requirement for these investigations is

given in Tables 3.2, 3.3 and 3.4, and depends on the presumed diagnosis. Potential medical workup for a differential diagnosis of MS [6] and for suspected acute transverse myelitis, in accordance with guidelines suggested by the Transverse Myelitis Consortium Working Group [4, 5], should be performed.

- (a) CSF analysis should be performed systematically. However, if the clinical features and MRI fulfil typical CIS/MS criteria, depending on the centre's protocol, CSF analysis may be optional. In other cases, CSF analysis must always be performed with isoelectric focusing of immunoglobulins (IgG) from both serum and CSF to look for oligoclonal bands.
- (b) Chest X-ray and urine analysis are usually performed to identify possible markers of systemic autoimmune disease or systemic extension of infection. These investigations are also commonly required before commencing high-dose methylprednisolone therapy or chemotherapy.
- (c) Screening for serum antinuclear antibodies, soluble antigen antibodies (SSA and SSB), anti-phospholipids, Lyme disease, *Treponema pallidum* haemagglutination assay-Venereal Disease Research Laboratory (TPHA-VDRL) and human immunodeficiency virus is usually done to eliminate the possible diagnosis of common autoimmune and infection-mediated disorders.
- (d) ECG, which is required before high-dose intravenous methylprednisolone or mitoxantrone treatment.

The other investigations listed in Tables 3.2, 3.3 and 3.4 should be performed on the basis of the clinical scenario.

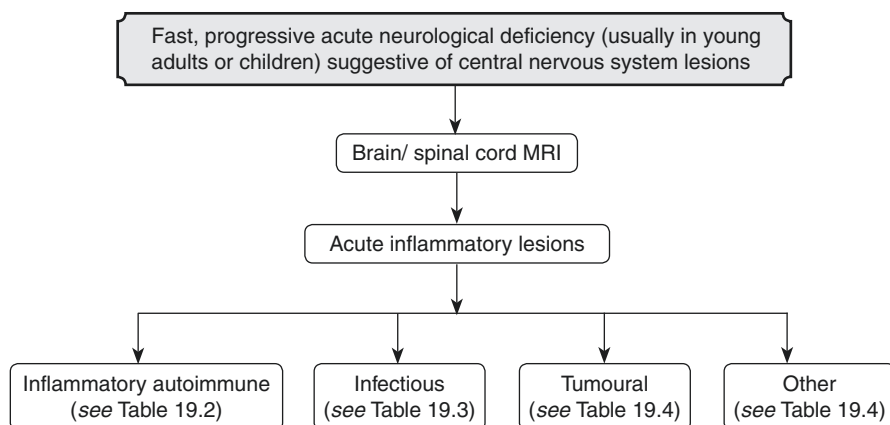
---

### **Causes: Which Diagnosis Best Fits the Clinical and Paraclinical Data?**

The most important demyelinating emergencies and the diagnostic strategy (Fig. 3.1) are discussed below. Other causes are given in Table 3.2.

### **Clues to a Diagnosis of MS (McDonald 2005, 2010 and 2017 Criteria, [8, 9] 2016 MAGNIMS MRI Criteria [10])**

A diagnosis of MS must be generated from both clinical or MRI evidence for dissemination in space (DIS) and dissemination in time (DIT). Different imaging and clinical criteria have been used for maximizing the likelihood of diagnosis. McDonald and MAGNIMS criteria [10] have been used increasingly in recent years. A prerequisite for evidence of MRI dissemination in space in the McDonald 2017 criteria is to be able to observe at least 1 lesion in at least 2 different suggestive locations: periventricular, juxtacortical, infratentorial or spinal cord. Symptomatic or asymptomatic gadolinium enhancing lesions or CSF oligoclonal bands can be considered for substitution of dissemination in time.



**Fig. 3.1** Diagnostic strategy flow chart

The size of the lesions, in all the above criteria, must be  $\geq 3$  mm.

Ovoid, sharp-edged cerebral lesions (especially periventricular, juxtacortical, in the vicinity of the corpus callosum or cerebellar peduncles) and ovoid lesions in the spinal cord with a partial and posterolateral location are highly suggestive of MS. Hypointense lesions on T<sub>1</sub>-WI appearing as 'black holes', which are indicative of old non-active lesions, are also characteristic features of MS. Brain atrophy and atrophy of the corpus callosum (best identified on sagittal MRI sequences) are also commonly observed radiological features of MS.

### MS Variants Presenting as Severe Acute Idiopathic Inflammatory Attacks [11, 12]

Balo concentric sclerosis (BCS) is a rare variant of MS but has also been described in patients with neuromyelitis optica spectrum disorders. The diagnosis is made histopathologically in the presence of a specific CNS lesion consisting of concentric rings of demyelination alternating with myelinated white matter [7]. This pattern is directly identifiable on contrast-enhanced MRI with separate rings of enhancement at sites of increased blood–brain barrier permeability. T<sub>2</sub>-weighted images also suggest separate zones of demyelination in a characteristic concentric pattern. Balo concentric lesions may run a fulminant course with very large lesions. The concentric pattern is indicative of myelin breakdown and blood–brain barrier permeability at various stages of development. Typical MS-like lesions may be associated with the Balo concentric lesions on the same brain MRI. BCS is more frequent in subjects of Asian origin, among people from Han Chinese and Filipino descent.

The Marburg variant of MS (a disease with an acute monophasic course, typically with large lesions in the cerebral hemispheres) has been described in the literature from old historic case reports. There is currently no specific definition of this condition; it presents as a very severe, destructive, tumefactive, CIS [13]. Lesions are typically more destructive than in ADEM and are characterized by massive macrophage infiltration, active demyelination, acute axonal injury and necrosis. Biopsy can help to confirm the demyelinating nature of the lesion, which typically has myelin-laden foamy macrophages intermingled with reactive astrocytes and variable perivascular and parenchymal lymphocytic inflammation, occasionally with some neutrophils. It is important to point out that the presence of Creutzfeldt–Peters cells (astrocytes with fragmented nuclear inclusions) can be mistaken for mitotic glial cells of tumoural origin [11]. These neuropathological characteristics may be found also in tumefactive lesions of neuromyelitis optica. Lesions may present with open-ring enhancement and peripheral restriction on diffusion-weighted imaging [14].

Tumefactive MS should be distinguished from the Marburg variant when dissemination occurs in space and time, with less destructive, concurrent, ‘typical’ periventricular and juxtacortical or infratentorial ovoid lesions. Ventricular enlargement and grey matter atrophy are also potential markers for MS. Open-ring enhancement and lack of mass effect are characteristic features of tumefactive demyelinating lesions in general.

Schilder myelinoclastic diffuse sclerosis has been described as a rare acute or subacute demyelinating disorder observed mainly in young patients. It presents as a symmetrical tumefactive demyelination mostly involving the centrum semiovale and the corpus callosum and its neuroradiological description frequently mimics leukodystrophies or a brain tumour. This entity based on old historical case reports also currently lacks a specific definition, which can be confounded by the Marburg variant of MS or, in some other aspects, by ADEM or severe isolated tumefactive demyelinating lesions [1, 2].

The descriptions of Marburg or Schilder lesions from historical publications do not permit the differentiation between the two and from tumefactive clinically isolated syndrome at risk for MS or other overlapping syndromes [2]. The pathological findings in all of these conditions suggest inflammatory demyelination of presumed autoimmune origin, and the distinction is usually clinically and pathologically relative rather than absolute [2, 13].

Recently the concept of isolated tumefactive demyelinating lesion (TDL) has been used to describe a tumefactive demyelinating spectrum disorder of presumed autoimmune origin underlying various overlapping syndromes [1].

The differential diagnoses of idiopathic transverse myelitis [4, 5, 15] and MS offer a broad view of the possible causes of acute demyelinating events. A review of an international expert panel board explored a consensus approach to develop guidelines on the subject [6].

## Clues to a Diagnosis of ADEM [16–19]

ADEM is commonly associated with atypical multiple symptoms and clinical presentation suggestive of more severe and diffuse brain impairment, such as altered consciousness, rapidly progressive encephalopathy, aphasia, apraxia, agnosia, seizures, fever, nausea or vomiting [19]. A depressed level of consciousness may be a more specific clinical criterion for pathologically confirmed ADEM than encephalopathy [18]. Bilateral optic neuritis involvement is possible. ADEM can occur at any age but is more common during childhood. Both sexes are affected with equal frequency. The overall mortality in ADEM is less than that in the Marburg variant of MS, and 80% of patients make a dramatic recovery with little or no residual functional impairment [11]. Oligoclonal bands are usually absent in the CSF. If otherwise positive (in one-third of cases), these oligoclonal bands should disappear from CSF controls after several months. Serum biological tests and inflammatory parameters are usually normal in blood. However, anti-MOG antibodies especially in children have been found in 40% of cases in some series [20], less commonly anti-AQP4 antibodies, rarely anti-NMDA antibodies and a few cases with anti-VGKC or anti-GlyR antibodies have been also reported [19, 21].

Peripheral nervous system involvement is frequent in ADEM, mainly with features of polyradiculoneuropathy, which occurs in 43% of patients in some series and may be at risk for recurrence of new neurological episode and associated with poorer prognosis [22, 23]. An absence of reflexes is predictive of a poor outcome after plasma exchange (PE) [24]. ADEM is typically a monophasic disease, but recurrent disseminated encephalomyelitis, which represents new relapses with atypical symptoms suggestive of ADEM may rarely occur [22]. An ADEM-like first event has been observed among patients of MS in more than one-third of cases in some series, if the follow-up is sufficiently long [16, 17]. No clinical or radiological features, and serum or CSF biomarkers can distinguish absolutely between ADEM and MS. However, the less typical the initial MS presentation, the less probable the subsequent evolution of relapses that confirm MS.

MRI studies have shown many useful characteristics that can help in distinguishing ADEM from MS [17, 25, 26]. These characteristics are usual diffuse lesions in the white and grey matter with suggestive (but not constant) involvement of the grey matter (mostly basal ganglia, thalamus and most specifically putamen [20]), very large pseudo-tumoural lesions or small disseminated lesions in ADEM. Although ADEM lesions (of a similar age) should all hypothetically enhance with gadolinium, this finding is rarely seen, and gadolinium enhancement may even be absent in about half of the reported cases [12, 19]. Possible normal MRI in the first 5 days to 8 weeks has been reported [19]. Lesions appear to be of similar age, may be confluent and fluffy, are usually less well delineated than the sharp-edged typical ovoid lesions observed in MS. ‘Sleeves’ of demyelination surround venules and are associated with significant inflammatory infiltrates dominated by macrophages, but the

extent of necrosis, axonal injury and demyelination is typically less marked than that in pseudo-tumoural MS or in Marburg lesions [11]. Confluent demyelination is the pathological hallmark of acute MS, whereas only perivenous demyelination is the hallmark of ADEM [18]. Luxol-fast blue myelin staining and MBP or PLP immunochemistry are mandatory to characterize demyelination pattern. A distinct pattern of cortical microglial activation (KIM1P immunochemistry) without cortical demyelination may be a pathological correlate of the depressed level of consciousness in ADEM [18]. However, it can be difficult to distinguish between these entities because of their frequent pathogenic overlap. This may be the case in ADEM associated with anti-MOG antibodies [27].

In the more severe cases of acute haemorrhagic leukoencephalitis, the inflammatory reaction is associated with perivascular haemorrhages, venous necrosis and severe brain oedema [17, 18]. These cases have been described as Weston Hurst acute haemorrhagic leukoencephalitis, which forms a spectrum of dramatic post-infectious ADEM with haemorrhagic components.

In children, preceding infection or vaccination, lack of periventricular lesions, the absence of black holes (suggestive of ancient lesions without oedema and contrast enhancement) and a diffuse bilateral lesion pattern were found to be risk factors for ADEM, in contrast to MS (Callen criteria) [16, 25, 28, 29]. ADEM is generally a monophasic disorder that typically occurs 6 days to 6 weeks following infection. However, unlike in MS, previous infection in adults has not been found to be a risk factor for ADEM [16, 17]. An international expert board proposed consensus definitions regarding the CNS inflammatory demyelinating disorders of children and adolescents with specific criteria for ADEM (International Pediatric Multiple Sclerosis Study Group (IPMSSG) 2007, revised in 2012) [30, 31]. De Seze et al. also proposed diagnostic criteria for ADEM in adults (Table 3.5) [16].

### Clues to a Diagnosis of Transverse Myelitis [4, 32]

Acute transverse myelopathy (ATM) may be defined as a focal inflammatory disorder of the spinal cord, resulting in a severe bilateral motor, sensory and autonomic dysfunction with a progression to nadir between 4 h and 21 days after the

**Table 3.5** Acute disseminated encephalomyelitis (ADEM) criteria in adults (De Seze criteria [11])

*Two of the three following criteria are required for the diagnosis of ADEM:*

1. At least one clinical atypical symptom of multiple sclerosis (MS): Alteration of consciousness, hypersomnia, seizures, acute cognitive impairment, hemiplegia, tetraplegia, aphasia, bilateral optic neuritis
2. Absence of oligoclonal bands in the cerebrospinal fluid
3. Grey matter involvement (basal ganglia or cortical lesions)

onset of symptoms. It should be differentiated from acute partial transverse myelitis, which is less severe. The definitions of these terms have been clarified by the Transverse Myelitis Consortium Working Group [5]. MRI typically demonstrates a large lesion occupying greater than half of the cross sectional area of the spinal cord with central grey matter involvement and frequently associated longitudinal extension covering more than two vertebral segments. Transverse myelitis is mostly of idiopathic autoimmune origin ('idiopathic acute transverse myelitis'), overlapping neuromyelitis optica spectrum disorders (NMOSD). Infectious or post-infectious determinants are also common (Table 3.3). See also Tables 3.2 and 3.4 for differential diagnosis.

### Clues to a Diagnosis of Devic/Neuromyelitis Optica (NMO) [2, 33]

NMO is a demyelinating disease more frequent in women (sex ratio F/M: 9/10) that preferentially affects the optic nerve and spinal cord, tends to present severe acute relapses and results in early permanent disability in most affected patients. The autoantibody marker NMO-IgG (anti-AQP4 IgG), which targets the water channel protein aquaporin-4, is found in 60–75% of cases and is highly specific for NMO. Brain MRI may be normal, but encephalitic lesions have occasionally been described, especially in the diencephalon and encephalic tumefactive lesions with specific loss of AQP4 demonstrated on immunochemistry performed in biopsy [34]. Anti-MOG antibodies may be found in around 15–25% of AQP4-IgG negative patients and are associated more often with bilateral anterior retrobulbar optic neuritis and thoracic myelitis with conus involvement, responsive to corticosteroids. Fluffy encephalic lesions overlapping ADEM are possible.

### Clues to a Diagnosis of Lymphoma [35]

This is probably one of the most difficult diagnoses that must be excluded. MRI usually shows a large lesion with intense homogeneous diffuse post-gadolinium enhancement with little mass effect, restricted diffusion and lipid peaks on spectroscopy. In some cases, several lesions may be found. *Corticosteroids should be avoided before biopsy*, if possible, because the lesion may resolve, disappear or show non-specific inflammation after treatment. Immunodeficiencies increase the risk of primary lymphoma of the CNS, but lymphoma is also described in immunocompetent patients. Epstein–Barr virus infection increases the risk only in immunodeficient and not in immunocompetent patients. An extensive search for extra-neuronal involvement is mandatory. A biopsy of the CNS lesion (or of a lesion elsewhere in the body) must be performed to confirm the diagnosis. Lymphocyte immunophenotypes and a search for a clonal lymphoproliferative expansion (usually of B lymphocytes) must be performed.



## Treatment of Acute Demyelinating Emergencies

### Treatment of Idiopathic Acute Inflammatory Demyelinating Attacks [36–38]

#### Corticosteroids

The North American and European guidelines for the treatment of MS relapses state that high-dose methylprednisolone should be considered as the first-line treatment for MS relapses (level of evidence 1) [39]. There is consistent evidence from several class I studies and meta-analyses of the beneficial effect of glucocorticoid treatment in relapses of MS. [38] Hence, treatment with intravenous or oral methylprednisolone at a dose of 1000 mg or 500 mg daily for 3–5 days should be considered for the treatment of relapses (good practice point; Multiple Sclerosis Therapy Consensus Group, 2004 [40]). However, in patients who fail to respond to therapy with methylprednisolone in the dose range used in randomized, placebo-controlled trials, treatment with higher doses (1 g daily up to 10 g, total dose) should be considered (level of evidence 3) [40]. This scheme is also used in neuromyelitis optica and ADEM [19].

#### Plasma Exchange (PE)

Evidence suggests that PEs are helpful for patients with severe attacks who do not improve after standard treatment with high-dose corticosteroids. This is in agreement with previous controlled trials and retrospective series associated with a clinically important improvement in the first weeks after PE in ~40% of patients with acute and severe attacks of CNS inflammatory demyelination who had not previously responded to high-dose corticosteroids [13, 24, 38, 41–43]. A trend towards early benefit (at 1 month after relapse treatment) was seen in 64% of relapsing/remitting patients in the double-blind study by Weiner et al., in which 76 patients were randomized to 11 true PEs or sham exchanges [43]. In this study, improvement was statistically significant only within the first 4 weeks of PEs (Expanded Disability Status Scale [EDSS] at 2 and 4 weeks' evaluation) compared with sham-treated controls. Patients treated with true PE had an estimated median recovery time of 4 weeks, whereas patients who received the sham exchange had a median recovery time of 13 weeks. The amount of worsening during the exacerbation was associated with a subsequent improvement during treatment. Improvement occurs early in the course of PEs in the first 2 weeks and is often sustained during follow-up [13]. Early treatment in the first 2 weeks after unresponsiveness to high-dose intravenous corticosteroids seems to be a predictor of improvement compared with delayed PE, but late improvement has also been reported in some patients [13, 24, 41]. Partial evidence indicates that MS patients with humoral/B lymphocyte immune-mediated pathology (pattern II; Keegan and Luccinetti et al. [44]) are more likely to respond favourably to PE. However, a biopsy is not performed routinely and is recommended only for differential diagnosis purposes, if needed. PE may also improve recovery



from corticosteroid-resistant relapses in patients with NMO, which is a humoral immune-mediated disease [45, 46].

The European Federation of Neurological Societies guidelines on the treatment of MS relapses state that PE is probably efficacious in a subgroup of patients with severe relapses who do not respond to methylprednisolone therapy, and it should be considered in this patient subgroup (level of evidence 2) [39]. PE may be used in the acute treatment of both MS variants and ADEM [13, 38, 54]. Plasmapheresis that does not require albumin replacement may be used instead of PE.

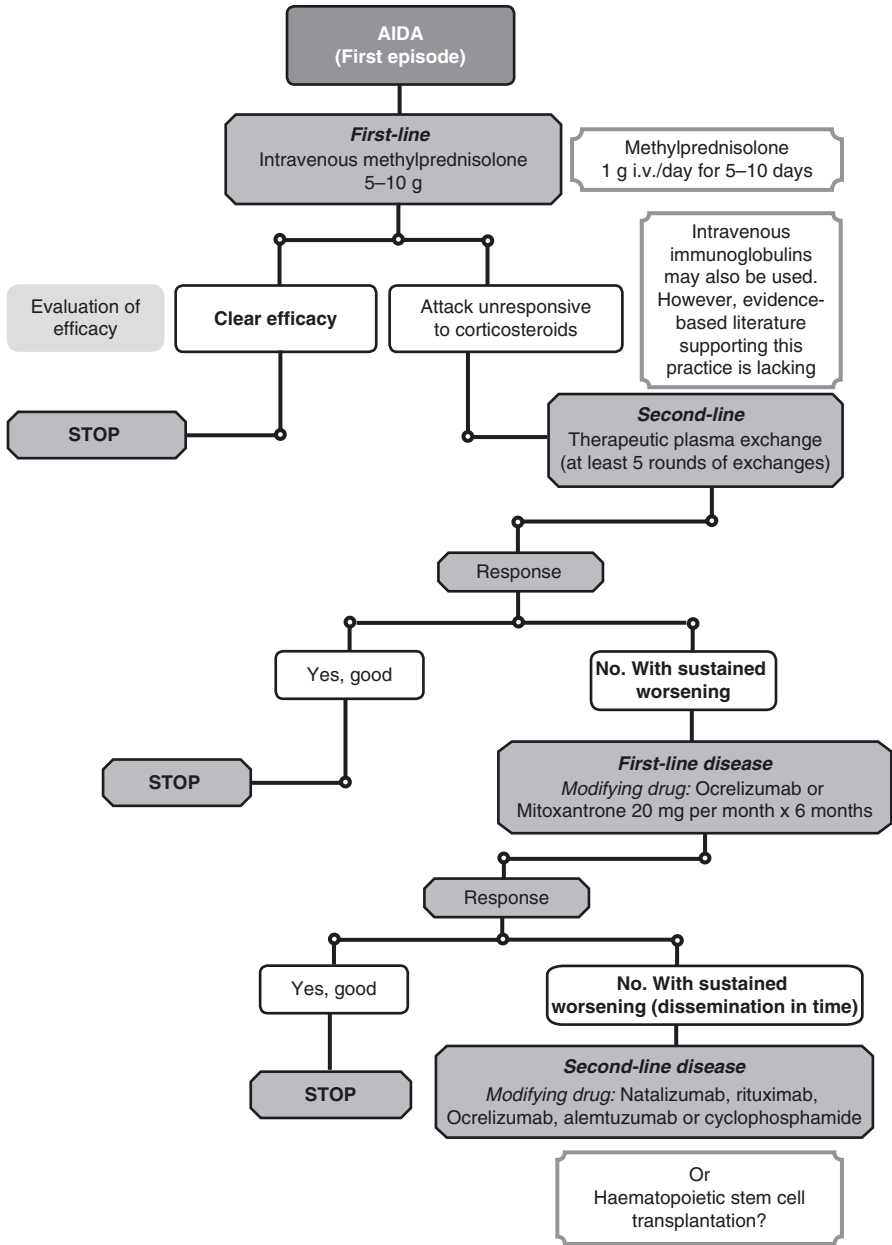
## Other Therapies

Several studies have investigated whether intravenous IG (i.v. IG) treatment as an add-on to therapy with high-dose intravenous methylprednisolone is superior to add-on placebo treatment of acute relapses. Although a few short retrospective series initially reported some benefits, larger and randomized studies showed negative results [39, 47]. The efficacy of i.v. IG in ADEM and severe optic neuritis has been demonstrated in a few, very small studies [17]. However, negative results were reported from a randomized controlled study, [48] and no other controlled randomized studies with positive results have been published on CNS idiopathic inflammatory demyelinating diseases [38]. Hence, contrary to current practices in peripheral nervous system inflammatory diseases, i.v. IG is less commonly used in CNS inflammatory acute attacks than PE [37]. Whereas treatment with natalizumab appears to lower the frequency of relapses in MS, it was not effective in the treatment of relapses in a randomized, placebo-controlled class I study of 180 patients with MS relapses [49]. Rituximab, ocrelizumab, mitoxantrone or other disease modifying drugs should not be used to treat acute attacks as these products need several months to demonstrate efficacy on clinical and MRI backgrounds but should be further discussed in case of relapses. One controlled randomized study of relapses of MS suggested that a multidisciplinary team rehabilitation programme may result in better functional recovery after 3 months compared with treatment with intravenous methylprednisolone alone [50].

## Therapeutic Strategy (Fig. 3.2)

This is an oversimplification of the therapeutic choices, but needs very careful planning and decision-making in an individual patient, with a detailed discussion on the risks and benefits of each therapy.

**First-Line** Methylprednisolone 1000 mg i.v. per day for 3 days. In case of severe neurological impairment, 5–10 days of i.v. methylprednisolone (1000 mg/day) may be used [37, 38, 51, 52].



**Fig. 3.2** Therapeutic algorithm to manage a threatening episode of acute inflammatory demyelinating attack (AIDA) of presumed autoimmune origin within the central nervous system

**Second-Line** PE may be performed in case of sustained worsening or an absence of improvement with methylprednisolone treatment after 7–10 days [13, 37, 41, 53, 54]. This treatment must not be delayed beyond several weeks, as its efficiency may worsen as time passes [41, 54]. At least 5–7 rounds of PEs (usually 2–3 l per exchange) are usually required [13, 37, 38, 41, 43, 53].

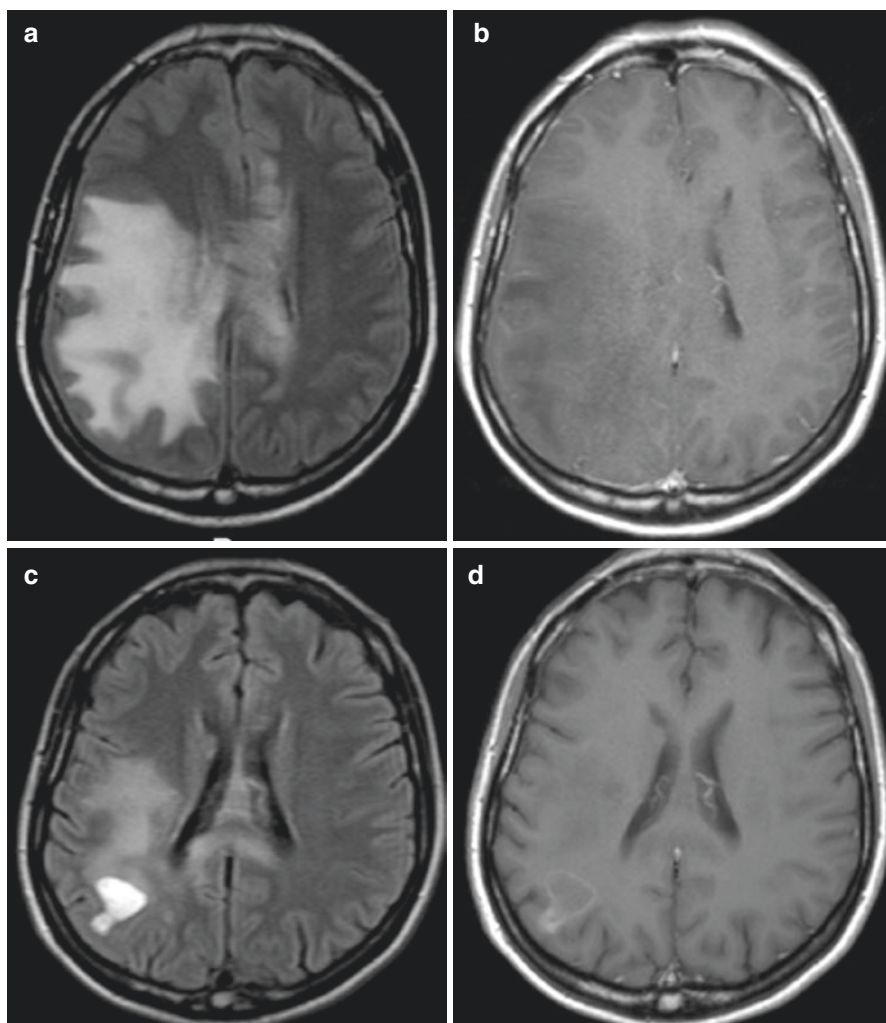
Some centres may use i.v. IG, but there is less evidence from the literature to support the effectiveness of i.v. IG in these conditions, with the possible exception of ADEM [17, 38].

**Third-Line** Ocrelizumab or Mitoxantrone 20 mg i.v. monthly for 6 months or 12 mg/m<sup>2</sup> monthly for 3 months and then every 3 months for a maximum of 1 year may be considered in case of new or sustained clinical worsening beyond 1 month (which is suggestive of dissemination in time) as this treatment is approved by most regulatory agencies for severe, rapidly disabling MS [38, 55]. In case of further severe recurrent attacks, cyclophosphamide [38] or monoclonal antibodies (natalizumab, alemtuzumab, rituximab and more recently ocrelizumab) may also be discussed. In an international survey, our group has shown that these modifying therapies are used by most MS centres after a first, acute CIS in cases of sustained severe worsening beyond 1 month, despite the use of corticosteroids and PE [37]. Intravenous cyclophosphamide has also been used with good results in a retrospective series of patients with SLE and Sjögren syndrome with acute inflammatory CNS involvement [56, 57]. Finally, for the most severe and treatment-resistant cases, a final treatment option may be autologous haematopoietic stem cell transplantation [38, 58].

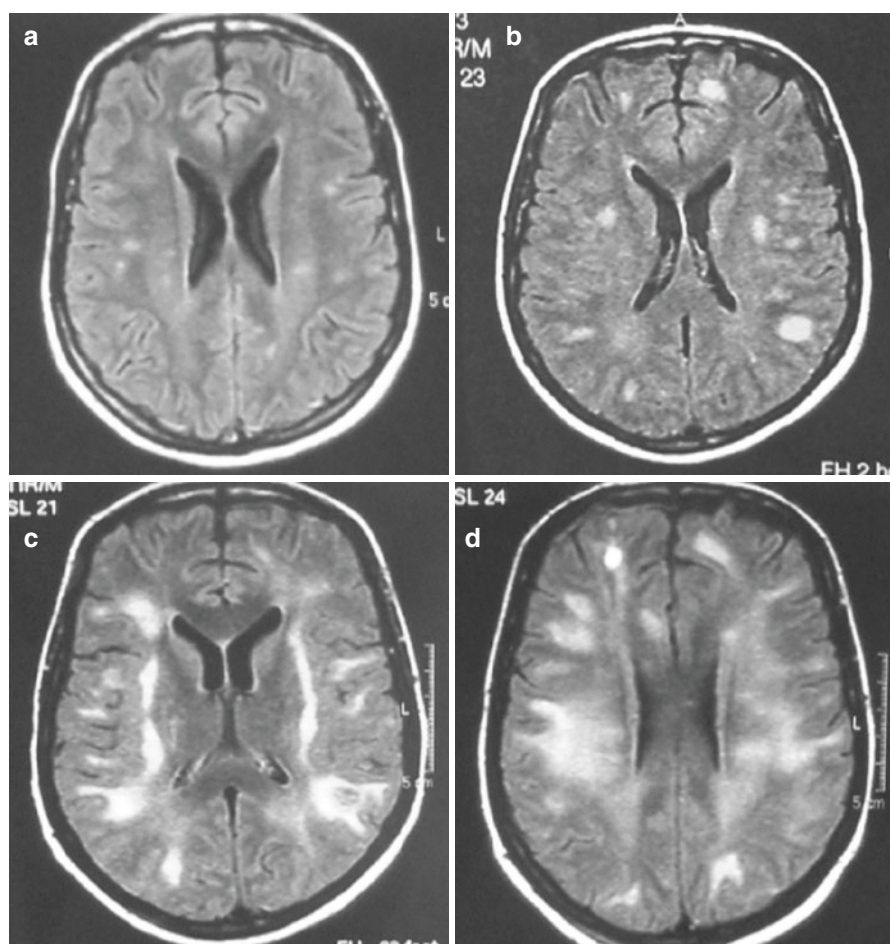
---

## Prognosis and Prognostic Markers

Clinical severity with pyramidal/spinal cord, cerebellar and brain stem involvement appears to be the main clinical prognostic marker during the acute phase of the demyelinating emergency. However, the clinical severity does not lead to subsequent evolution or relapses and MS. Severe inflammatory demyelinating attacks are usually monophasic and may result in severe definitive impairment [19, 59]. However, the final recovery may also be good in the long term. Very large MRI lesions may be dramatically reduced in controls several weeks after the initiation of treatment (Fig. 3.3). In other cases, the acute evolution may be fatal (Fig. 3.4). In contrast, CISs at high risk for relapses and MS are often less severe during the acute phase but may be associated with a worse functional long-term outcome.



**Fig. 3.3** A 39-year-old woman presenting with a large monofocal tumour-like demyelinating plaque in the centrum ovale FLAIR (a) with only very little enhancement on T<sub>1</sub> post-gadolinium WI (b). Biopsy demonstrated the inflammatory demyelinating nature of the lesion with inflammatory infiltrates dominated by myelin-laden foamy macrophages intermingled with reactive astrocytes and very scarce CD20 immuno-staining of lymphocytes, ruling out a lymphoma. The clinical condition of the patient (left side hemiplegia with neuropsychological disturbances) dramatically improved after ten infusions of 1 g i.v. methylprednisolone followed by seven rounds of plasma exchanges. The control MRI performed 1 month after the first imaging showed a dramatic decrease of the lesion volume on FLAIR (c) and T<sub>1</sub> after gadolinium imaging (d). The position of the biopsy is visible at the rear of the lesion



**Fig. 3.4** A woman, 27 years of age, was referred for status epilepticus and gait disturbances and thereafter progressive worsening with ataxia and encephalopathy. Multiple small lesions disseminated throughout the brain and spinal cord coalesce to form large confluent white-matter plaques and widespread diffuse demyelination throughout the white matter (FLAIR WI): initial MRI (a), next MRI 2 weeks (b), 6 weeks (c) and 2 months later (d). Despite the acute lesions, there was no T<sub>1</sub> gadolinium enhancement. CSF showed 1 leucocyte, 0.5 g/L protein and positive IgG oligoclonal bands. An extensive biology check-up was normal. The patient died several months after the first clinical signs, despite 2 rounds of 5 g i.v. methylprednisolone, 7 plasma exchanges and i.v. cyclophosphamide. Neuropathology was performed and revealed extensive typical sharp-edged demyelinating multiple sclerosis lesions throughout the CNS

## Conclusion

Acute demyelinating emergencies usually appear as rapidly evolving inflammatory attacks of the CNS in young adults. Clinical evaluation, MRI, serum (mostly anti-AQP4 IgG and anti-MOG IgG) and CSF investigations are necessary for determining the aetiology, which is often of idiopathic autoimmune origin. High-dose intravenous methylprednisolone and PE, if needed, are the main treatment modalities during the acute phase.

## References

1. Siri A, Carra-Dalliere C, Aygnac X, Pelletier J, Audoin B, Pittion-Vouyovitch S, Debouverie M, Lionnet C, Viala F, Sablot D, Brassat D, Ouallet J-C, Ruet A, Brochet B, Taillandier L, Bauchet L, Derache N, Defer G, Cabre P, de Seze J, Lebrun Frenay C, Cohen M, Labauge P. Isolated tumefactive demyelinating lesions: diagnosis and long-term evolution of 16 patients in a multicentric study. *J Neurol*. 2015;262(7):1637–45.
2. Hardy TA, Reddel SW, Barnett MH, Palace J, Lucchinetti CF, Weinshenker BG. Atypical inflammatory demyelinating syndromes of the CNS. *Lancet Neurol*. 2016;15(9):967–81.
3. Confavreux C, Vukusic S. The clinical epidemiology of multiple sclerosis. *Neuroimaging Clin N Am*. 2008;18:589–622.
4. Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. *Semin Neurol*. 2008;28:105–20.
5. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology*. 2002;59:499–505.
6. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler*. 2008;14:1157–74.
7. Ouallet J-C, Bodiguel E, Bensa C, Blanc F, Brassat D, Laplaud D, Zephir H, de Seze J, Magy L, Groupe de Re'flexion sur la Scl'rose en Plaques: GRESE. Recommendations for useful serum testing with suspected multiple sclerosis. *Rev Neurol (Paris)*. 2013;169(1):37–46.
8. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. *Ann Neurol*. 2005;58:840–6.
9. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.
10. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, Rovira A, Sastre-Garriga J, Tintorè M, Frederiksen JL, Gasperini C, Palace J, Reich DS, Banwell B, Montalban X, Barkhof F, MAGNIMS Study Group. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol*. 2016;15(3):292–303.
11. Hu W, Lucchinetti CF. The pathological spectrum of CNS inflammatory demyelinating diseases. *Semin Immunopathol*. 2009;31:439–53.
12. Capello E, Mancardi GL. Marburg type and Balò's concentric sclerosis: rare and acute variants of multiple sclerosis. *Neurol Sci*. 2004;25(Suppl 4):S361–3.



13. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol*. 1999;46:878–86.
14. Lucchinetti CF, Gavrilova RH, Metz I, et al. Clinical and radiographic spectrum of pathologically-confirmed tumefactive multiple sclerosis. *Brain*. 2008;131:1759–75.
15. De Seze J, Lanctin C, Lebrun C, et al. Idiopathic acute transverse myelitis: application of the recent diagnostic criteria. *Neurology*. 2005;65:1950–3.
16. De Seze J, Debouverie M, Zephir H, et al. Acute fulminant demyelinating disease: a descriptive study of 60 patients. *Arch Neurol*. 2007;64:1426–32.
17. Young NP, Weinshenker BG, Lucchinetti CF. Acute disseminated encephalomyelitis: current understanding and controversies. *Semin Neurol*. 2008;28:84–94.
18. Young NP, Weinshenker BG, Parisi JE, et al. Perivenous demyelination: association with clinically defined acute disseminated encephalomyelitis and comparison with pathologically confirmed multiple sclerosis. *Brain*. 2010;133:333–48.
19. Berzero G, Cortese A, Ravaglia S, Marchioni E. Diagnosis and therapy of acute disseminated encephalomyelitis and its variants. *Expert Rev Neurother*. 2016;16(1):83–101.
20. Koelman DLH, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. *J Neurol*. 2015;262(9):2013–24.
21. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M, Singh G, Cobo Calvo A, Kaida K, Morales PS, Wirtz PW, Yamamoto T, Reindl M, Rosenfeld MR, Graus F, Saiz A, Dalmau J. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;75(3):411–28.
22. Marchioni E, Ravaglia S, Piccolo G, et al. Postinfectious inflammatory disorders: subgroups based on prospective follow-up. *Neurology*. 2005;65:1057–65.
23. Marchioni E, Ravaglia S, Montomoli C, Tavazzi E, Minoli L, Baldanti F, Furione M, Alfonsi E, Bergamaschi R, Romani A, Piccolo L, Zardini E, Bastianello S, Pichiecchio A, Ferrante P, Delbue S, Franciotta D, Bono G, Ceroni M. Postinfectious neurologic syndromes a prospective cohort study. *Neurology*. 2013;80(10):882–9.
24. Llufríu S, Castillo J, Blanco Y, et al. Plasma exchange for acute attacks of CNS demyelination: predictors of improvement at 6 months. *Neurology*. 2009;73:949–53.
25. Callen DJ, Shroff MM, Branson HM, et al. Role of MRI in the differentiation of ADEM from MS in children. *Neurology*. 2009;72:968–73.
26. Ketelslegers IA, Neuteboom RF, Boon M, Catsman-Berrevoets CE, Hintzen RQ, Dutch Pediatric MS Study Group. A comparison of MRI criteria for diagnosing pediatric ADEM and MS. *Neurology*. 2010;74(18):1412–5.
27. Di Pauli F, Höftberger R, Reindl M, Beer R, Rhomberg P, Schanda K, Sato D, Fujihara K, Lassmann H, Schmutzhard E, Berger T. Fulminant demyelinating encephalomyelitis: insights from antibody studies and neuropathology. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(6):e175.
28. Chabas D, Pelletier D. Sorting through the pediatric MS spectrum with brain MRI. *Nat Rev Neurol*. 2009;5:186–8.
29. Peche SS, Alshekhlee A, Kelly J, Lenox J, Mar S. A long-term follow-up study using IPMSSG criteria in children with CNS demyelination. *Pediatr Neurol*. 2013;49(5):329–34.
30. Krupp LB, Banwell B, Tenenbaum S, International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology*. 2007;68:S7–S12.
31. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, Ghezzi A, Hintzen R, Kornberg A, Pohl D, Rostasy K, Tenenbaum S, Wassmer E, International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler*. Sep. 2013;19(10):1261–7.
32. Pandit L. Transverse myelitis spectrum disorders. *Neurol India*. 2009;57:126–33.
33. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6:805–15.

34. Popescu BFG, Guo Y, Jentoft ME, Parisi JE, Lennon VA, Pittock SJ, Weinshenker BG, Wingerchuk DM, Giannini C, Metz I, Brück W, Shuster EA, Carter J, Boyd CD, Clardy SL, Cohen BA, Lucchinetti CF. Diagnostic utility of aquaporin-4 in the analysis of active demyelinating lesions. *Neurology*. 2015;84(2):148–58.
35. Hagavathi S, Wilson JD. Primary central nervous system lymphoma. *Arch Pathol Lab Med*. 2008;132:1830–4.
36. Tumani H. Corticosteroids and plasma exchange in multiple sclerosis. *J Neurol*. 2008;255(Suppl 6):36–42.
37. El Alaoui S, Brochet B, Ouallet JC. Modifying therapies used in severe first idiopathic acute inflammatory events within the central nervous system. *Neurology*. 2009;72(Suppl 3):A36.
38. McDaniel LM, Fields JD, Bourdette DN, et al. Immunomodulatory therapies in neurologic critical care. *Neurocrit Care*. 2010;12:132–43.
39. Sellebjerg F, Barnes D, Filippini G, et al. EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses. *Eur J Neurol*. 2005;12:939–46.
40. Multiple Sclerosis Therapy Consensus Group. Escalating immunotherapy of multiple sclerosis. *J Neurol*. 2004;251:1329–39.
41. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology*. 2002;58:143–6.
42. Rodriguez M, Karnes WE, Bartleson JD, et al. Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. *Neurology*. 1993;43:1100–4.
43. Weiner HL, Dau PC, Khatir BO, et al. Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. *Neurology*. 1989;39:1143–9.
44. Keegan M, König F, McClelland R, et al. Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange. *Lancet*. 2005;366:579–82.
45. Watanabe S, Nakashima I, Misu T, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. *Mult Scler*. 2007;13:128–32.
46. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke K-D, Wegner B, Hellwig K, Pache F, Ruprecht K, Havla J, Krumbholz M, Kümpfel T, Aktas O, Hartung H-P, Ringelstein M, Geis C, Kleinschnitz C, Berthele A, Hemmer B, Angstwurm K, Stellmann J-P, Schuster S, Stangel M, Lauda F, Tumani H, Mayer C, Zeltner L, Ziemann U, Linker R, Schwab M, Marziniak M, Bergh FT, Oy U H-v, Neuhaus O, Winkelmann A, Marouf W, Faiss J, Wildemann B, Paul F, Jarius S, Trebst C, Neuromyelitis Optica Study Group. Neuromyelitis optica: evaluation of 871 attacks and 1153 treatment courses. *Ann Neurol*. 2016;79(2):206–16.
47. Fazekas F, Lublin FD, Li D, et al. Intravenous immunoglobulin in relapsing–remitting multiple sclerosis: a dose-finding trial. *Neurology*. 2008;71:265–71.
48. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. *Neurology*. 2005;64:804–10.
49. O'Connor PW, Goodman A, Willmer-Hulme AJ, et al. Randomized multicenter trial of natalizumab in acute MS relapses. Clinical and MRI effects. *Neurology*. 2004;62:2038–43.
50. Craig J, Young CA, Ennis M, et al. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. *J Neurol Neurosurg Psychiatry*. 2003;74:1225–30.
51. Miller DM, Weinstock-Guttman B, Béthoux F, et al. A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. *Mult Scler*. 2000;6:267–3.
52. Marchioni E, Marinou-Aktipi K, Uggetti C, et al. Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. *J Neurol*. 2002;249:100–4.
53. Ruprecht K, Klinker E, Dintelmann T, et al. Plasma exchange for severe optic neuritis: treatment of 10 patients. *Neurology*. 2004;63:1081–3.
54. Bonnan M, Cabre P. Plasma exchange for severe attacks in the spectrum of central demyelinating disorders. In: Atta-ur-Rahman, editor. *Frontiers in clinical drug research: CNS and neurological disorders*, Vol. 2, Chapter: 3. Sharjah: Bentham Science; 2013. p. 55–109.



55. Scott LJ, Figgitt DP. Mitoxantrone: a review of its use in multiple sclerosis. *CNS Drugs*. 2004;18:379–96.
56. De Seze J, Delalande S, Fauchais AL, et al. Myelopathies secondary to Sjögren's syndrome: treatment with monthly intravenous cyclophosphamide associated with corticosteroids. *J Rheumatol*. 2006;33:709–11.
57. Neuwelt CM, Lacks S, Kaye BR, et al. Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. *Am J Med*. 1995;98:32–41.
58. Atkins HL, Bowman M, Allan D, Anstee G, Arnold DL, Bar-Or A, Bence-Bruckler I, Birch P, Bredeson C, Chen J, Fergusson D, Halpenny M, Hamelin L, Huebsch L, Hutton B, Laneuville P, Lapierre Y, Lee H, Martin L, McDiarmid S, O'Connor P, Ramsay T, Sabloff M, Walker L, Freedman MS. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet*. 2016;388(10044):576–85.
59. Debette S, de Sèze J, Pruvo JP, et al. Long-term outcome of acute and subacute myelopathies. *J Neurol*. 2009;256:980–8.

# Acute Non-traumatic Myelopathies

# 4

K. Venkatraman, N. Thamil Pavai,  
and R. Lakshmi Narasimhan

## Introduction

Acute and chronic disorders of the spinal cord produce a number of distinctive syndromes which relate to its special anatomical and physiological features. These unique clinical syndromes usually indicate a specific underlying etiology.

## Anatomical Overview

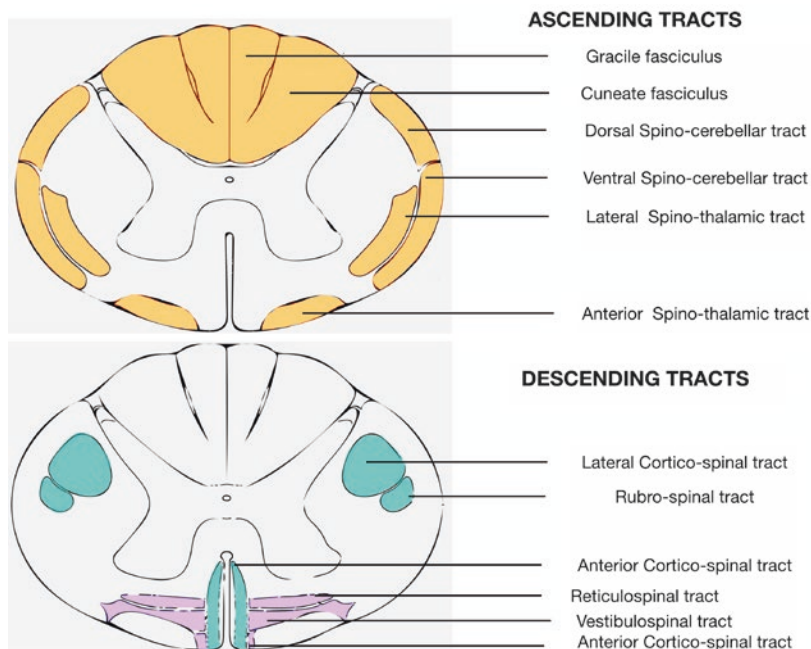
To provide a clearer framework of these clinical–anatomical syndromes, a brief review of the anatomy of the spinal cord is given in Fig. 4.1.

The cord is cylindrical in shape and slightly flattened dorsoventrally. It shows two localized enlargements—the cervical and lumbosacral. The central gray matter of the spinal cord is divided into a posterior column (horn), a lateral column (horn), and an anterior column (horn). Likewise, the peripheral white matter of the cord is divided into posterior, lateral, and anterior funiculi. Cells in the posterior horn of the gray matter serve sensory functions and those in the anterior horn serve motor functions. The lateral or intermediate horn subserves autonomic functions.

The white matter of the cord consists of ascending and descending tracts of nerve fibers. The ascending sensory pathways transmit both conscious and non-conscious sensory information. The sensory pathway segregates fibers into medial large myelinated fibers carrying fine touch and proprioception, and lateral small unmyelinated fibers. The large nerve fibers in the dorsal column form a lamination with the medial fibers originating from the lower extremity and trunk, ascending as the fasciculus gracilis. The lateral fibers carry sensory information from the upper trunk and limb, ascending as the fasciculus cuneatus. The dorsal columns ascend to the medulla, where they synapse in the gracile and cuneate nuclei, respectively. The second-order

---

K. Venkatraman · N. T. Pavai · R. L. Narasimhan (✉)  
Institute of Neurology, Madras Medical College, Chennai, Tamil Nadu, India



**Fig. 4.1** Diagrammatic representation of a transverse section of the spinal cord at mid-cervical level, showing the general arrangement of ascending and descending tracts

neurons then cross the midline in the medulla and ascend as the medial lemniscus to terminate in the thalamus. The smaller nerve fibers carrying pain and temperature form the anterolateral spinothalamic tract [1]. The axons forming these tracts cross to the opposite side of the cord in the anterior commissure and are thereafter located anterolaterally. The lateral spinothalamic tract is somatotopically organized, with cervical representation being the most medial, and sacral the most lateral.

The spinocerebellar tracts transmit non-conscious proprioception. The posterior spinocerebellar tract, which occupies the lateral funiculus, carries information from the lower limbs. The anterior spinocerebellar tract also occupies the lateral funiculus and carries afferents from the body. The cuneocerebellar tract carries proprioceptive impulses mainly from the arms, head, and neck. The other ascending tracts are the spino-tectal tract, which ends in the superior colliculus, and the spino-olivary tract, which projects to the inferior olivary nucleus.

The long descending tracts of the cord control and influence motor function. Almost 90% of the fibers of the corticospinal tract cross in the pyramidal decussation, giving rise to the lateral corticospinal tract in the spinal cord. The tract is somatotopically organized with fibers destined for the cervical area being medial and those for the sacral area being lateral. The remaining fibers descend adjacent to the anterior median fissure as the anterior corticospinal tract; they innervate the axial muscles. The other descending tracts (reticulospinal, tecto-spinal, vestibulospinal, rubrospinal) are all involved in the involuntary control of muscles.

The spinal cord is vascularized by longitudinally oriented anterior and posterior spinal arteries, which are reinforced by contributions from a number of smaller radicular arteries. A rich arterial plexus arises from interconnections between these blood vessels all along the pial surface of the cord. Medullary vessels originating from this plexus then enter the substance of the cord [1]. The single anterior spinal artery arises from the union of the anterior spinal branches of the vertebral artery. It then descends within the anterior median fissure of the spinal cord. It supplies most of the anterior two-thirds of the cord. Its smallest caliber is at the thoracic area, which is considered its watershed area. The two posterior spinal arteries arise from the vertebral arteries and descend along the posterolateral sulcus on either side of the spinal cord. The radicular arteries also enter every intervertebral foramen and supply the corresponding nerve roots [1].

The venous drainage of the cord is by the longitudinal anterior and posterior spinal veins. They are interconnected by a circumferentially arranged venous anastomosis on the surface of the cord. Small radicular veins drain the nerve roots segmentally.

---

## Spinal Cord Syndromes

A syndrome represents a group of signs and symptoms that appear in combination. A number of disorders affecting the cord present with distinctive syndromes, largely as a result of the specific anatomical and physiological organization of the cord. The different cord syndromes can be classified as follows:





1. Complete or incomplete transection syndrome (including the combined radicular and transverse cord syndrome)
2. Hemicord syndrome (Brown-Séquard syndrome)
3. Ventral cord syndrome (anterior spinal artery syndrome)
4. Central cord syndrome
5. Posterior column syndrome
6. Posterior lateral syndrome
7. Anterior horn cell syndrome
8. Anterior horn cell–pyramidal combined syndrome
9. Conus medullaris—cauda equina syndrome.

It should be noted that certain diseases present preferentially with specific syndromes.

Etiologically, the complete transection syndrome is associated with an inflammatory etiology (e.g., post-infectious/postvaccinial/multiple sclerosis [MS]), tumor, or trauma. Acute transverse myelitis is the prototype entity in this group. Hemicord syndromes are most often caused by either trauma or intramedullary tumors. The anterior spinal artery syndrome is chiefly attributable to vascular causes. The central cord syndromes are usually insidious intramedullary illnesses; syringomyelia is the prototypic lesion in this category. Posterior column syndromes are either tabetic (syphilitic) or rarely a presentation of MS. Posterior lateral syndromes are mostly insidious and the prototypic disease in this category is subacute combined degeneration caused by vitamin B<sub>12</sub> deficiency.

The anterior horn cell syndrome is characterized by flaccid paralysis and fasciculations. Anterior poliomyelitis is the prototypic illness. The anterior horn cell–pyramidal combined syndrome is exemplified by amyotrophic lateral sclerosis. The cauda conus syndromes are most often caused by trauma or intervertebral disc prolapse. Conus lesions are usually sudden and bilateral, whereas purely cauda equina lesions tend to be insidious and unilateral. Some of the important spinal cord syndromes are tabulated below (Table 4.1).

**Table 4.1** Some important spinal cord syndromes

Cord syndrome	Etiology	Clinical features	Diagrammatic representation
1. Cord transection (complete or incomplete)	<ul style="list-style-type: none"> <li>• Post-infectious</li> <li>• Multiple sclerosis</li> <li>• Trauma</li> <li>• Tumor</li> <li>• Epidural abscess or haematoma</li> <li>• Disc prolapse</li> </ul>	<p>Sensory loss and motor weakness below the level of lesion</p> <p>Sensory level for pinprick and radicular pain indicate level of lesion</p>	
2. Brown–Séquard syndrome (hemisection of the cord)	<ul style="list-style-type: none"> <li>• Intramedullary tumors</li> <li>• Trauma</li> </ul>	<p>Loss of pain and temperature contralateral to the side of lesion, sensory level is one or two segments below the level of the lesion</p> <p>Ipsilateral loss of proprioceptive function and ipsilateral weakness below the lesion</p>	
3. Anterior spinal artery syndrome	<ul style="list-style-type: none"> <li>• Aortic dissection</li> <li>• Thoracic, aortic surgery</li> <li>• Decompression sickness</li> <li>• Vasculitis</li> </ul>	<p>Abrupt onset of deficit.</p> <p>Back pain, flaccid paralysis with bowel and bladder involvement</p> <p>Posterior column sensations spared</p>	
4. Central cord syndrome	<ul style="list-style-type: none"> <li>• Intramedullary tumors</li> <li>• Syringomyelia</li> <li>• Trauma</li> </ul>	<p>Insidious onset</p> <p>Loss of pain and temperature with preservation of vibration, proprioception, and touch</p> <p>Late anterior horn involvement</p>	
5. Posterior column syndrome	<ul style="list-style-type: none"> <li>• Epidural compression</li> <li>• Neurosyphilis</li> </ul>	<p>Sensory ataxia due to loss of position and vibration sense below level of lesion</p>	
6. Anterior horn cell syndrome	<ul style="list-style-type: none"> <li>• Poliomyelitis</li> <li>• Post-irradiation</li> <li>• Spinal muscular atrophies</li> </ul>	<p>Ipsilateral flaccid paralysis with atrophy and fasciculations</p>	

## Acute Transverse Myelitis

Acute transverse myelitis (ATM) is a clinical syndrome characterized by a sudden onset of weakness and sensory loss, generally in a symmetrical pattern, below the affected spinal segment. Pathologically, the lesion usually involves many spinal cord segments. In most cases the primary process is a demyelinating one; however, necrosis is also sometimes seen [2]. The disorder is considered to be immunologically mediated in a majority of patients, because of its propensity to be preceded by vaccination (influenza, smallpox, polio, rabies, tetanus) or by a specific viral disease (mumps, measles, chicken pox). Rarely, transverse myelitis may result from spinal cord infection caused by herpes simplex virus—types 1 or 2, varicella zoster virus, cytomegalovirus, or Epstein–Barr virus. This type of direct infection usually affects immunologically compromised patients [3]. In other cases the antecedent factor remains a mystery.

## Incidence and Prevalence

Acute transverse myelitis has an incidence of 1–4 new cases per million people per year. It affects individuals of all ages; the age-related incidence shows bimodal peaks. The first peak is seen in children at the ages of 10–19 years, and the second involves adults in their fourth decade of life [4].

## Clinical Features

Acute transverse myelitis is characterized clinically by acutely or subacutely developing symptoms and signs of neurological dysfunction involving motor, sensory, and autonomic nerves and nerve tracts within the spinal cord. The upper thoracic cord is the most commonly involved site. A well-defined upper border of sensory dysfunction, [4] usually over the trunk, is often evident. At the maximal intensity of deficit, ~50% of patients would have lost almost all movements of their lower limbs, practically all patients would have bladder dysfunction and a majority of patients would have sensory abnormalities in the form of numbness or paresthesias [4]. Autonomic symptoms, such as bowel or bladder incontinence, increased urinary frequency, difficulty or inability to void, and constipation also occur frequently.

Several case series of this disorder reveal that up to one-third of patients improve with minimal or no sequelae, approximately one-third have a moderate amount of permanent disability and the remainder continue to have severe disabilities [4]. Rapid progression of symptoms, spinal shock and back pain have been shown to be predictive of poor recovery [4]. Predictors of poor outcome in children are female sex, severity of myelitis at onset, gadolinium enhancement of the spinal cord lesion,

absence of CSF pleocytosis, and absence of cervical cord involvement [5]. ATM can be divided into acute complete (ACTM) and acute partial transverse myelitis (APTM) based on the presentations. APTM is more likely to develop into multiple sclerosis [6]. In MS patients presenting with ATM sensory symptoms predominate with a relative sparing of motor system. On the basis of the likely etiology, ATM can be further classified into the following subtypes: [7]

1. Cases related to MS
2. Systemic disease (especially autoimmune-like systemic lupus erythematosus [SLE], Sjögren's syndrome, etc.)
3. Spinal cord infarction
4. Delayed radiation myelopathy
5. Infectious
6. Parainfectious
7. Idiopathic.

Age and gender may be considered useful to determine etiology in a patient presenting with TM syndrome. Spinal infarcts are more common in elderly and

**Table 4.2** Proposed diagnostic criteria and nosology of acute transverse myelitis [4]

<i>Inclusion criteria</i>
<ul style="list-style-type: none"> <li>• Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord</li> <li>• Bilateral signs and/or symptoms (though not necessarily symmetrical)</li> <li>• Clearly defined sensory level</li> <li>• Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)</li> <li>• Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and LP evaluation 2–7 days following symptom onset</li> <li>• Progression to nadir between 4 h and 21 days following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)</li> </ul>
<i>Exclusion criteria</i>
<ul style="list-style-type: none"> <li>• History of previous radiation to the spine within the past 10 years</li> <li>• Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery</li> <li>• Abnormal flow voids on the surface of the spinal cord consistent with AVM</li> <li>• Serological or clinical evidence of connective tissue disease (sarcoidosis, Behçet disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)</li> <li>• CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, mycoplasma, other viral infections (e.g., HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)</li> <li>• Brain MRI abnormalities suggestive of MS</li> <li>• History of clinically apparent optic neuritis</li> </ul>
Do not exclude disease-associated ATM

Adapted from [4]

*HIV* human immunodeficiency virus, *HTLV-1* human T-lymphotropic virus 1, *HSV-2* herpes simplex virus-2

*VZV* varicella zoster virus, *EBV* Epstein–Barr virus, *CMV* cytomegalovirus, *HHV-6* human herpesvirus-6

inflammatory etiology more common in females [6]. The diagnostic criteria for idiopathic ATM are listed in Table 4.2. A possible diagnosis of idiopathic ATM can be made if all inclusion criteria are fulfilled [4] and all exclusion criteria are negative. A diagnosis of secondary or disease-associated ATM can be made if all inclusion criteria are met and the patient identified as having an underlying disease [4].

## Investigations

Preliminary evaluation of an individual with an evolving spinal cord lesion should determine whether a structural cause (e.g., herniated disc, vertebral fracture, metastasis, or spondylolisthesis) can be identified [4]. MRI with gadolinium contrast should be obtained at the earliest (Fig. 4.2) [4]. If an urgent MRI is not possible, CT-myelography is a practical alternative [4]. If the causative factor is a surgically remediable pathology, an urgent neurosurgical evaluation is mandatory.

Based on the MRI picture, ATM can be classified as longitudinally extensive transverse myelitis (LETM) (>3 contiguous spinal cord segment) and short segment lesions. LETM is associated with NMO, idiopathic monophasic TM, and non-NMO recurrent TM, Sjögren's syndrome, SLE, sarcoidosis, neuro-Behçet disease, and parainfectious myelitis [8].

A lumbar puncture should be performed when imaging studies fail to reveal a structural cause, so that an inflammatory myelopathy can be distinguished from a non-inflammatory one. The CSF (cerebrospinal fluid) is evaluated by routine biochemical and pathological studies (cytology, protein, glucose), as well as for intrathecal antibody synthesis (oligoclonal bands and IgG index). CSF

**Fig. 4.2** MRI spine, T<sub>2</sub>W sagittal section showing intraspinal hyperintensity suggestive of acute transverse myelitis





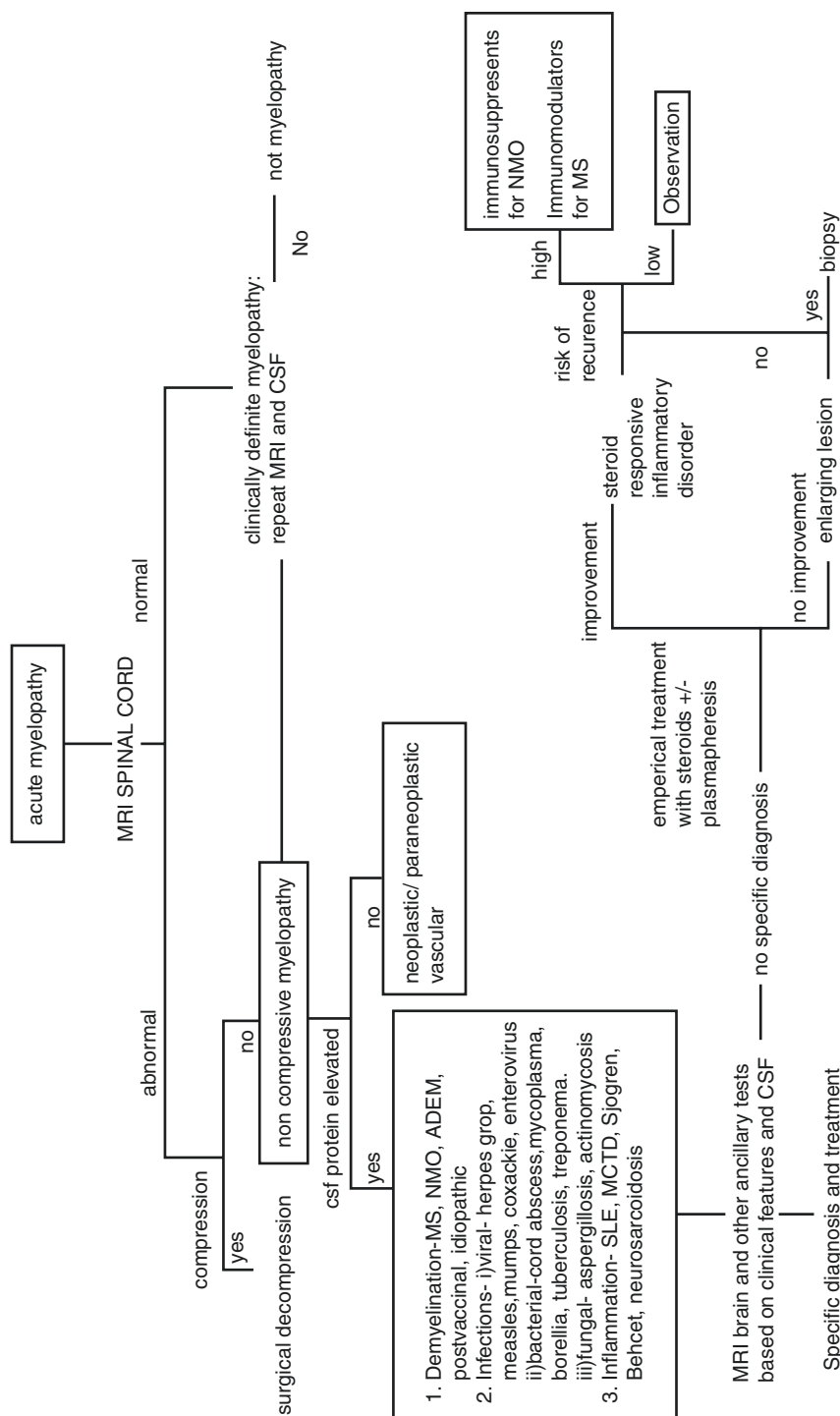
pleocytosis  $>30$  cells/mm<sup>3</sup> has a high likelihood of cause other than MS. In patients with APTM presence of CSF oligoclonal band rules out parainfectious and vascular cause and predicts a 90% transition rate to MS [6]. If the CSF studies also prove to be inconclusive, a non-inflammatory etiology should be considered. Likely causes of a non-inflammatory myelopathy include ischemia (arterial, venous, arteriovenous malformations [AVMs], or watershed ischemia), epidural lipomatosis, fibrocartilaginous embolism, and radiation injury [4]. For patients with subacute myelopathies, an elevated CSF leukocyte count (greater than 10 cells/mm<sup>3</sup>) is possibly useful in identifying patients with inflammatory myelopathies (including TM) as opposed to those with spinal cord infarcts [6]. If an inflammatory myelopathy is recognized, the extent of involvement of the nervous system should be determined. Imaging studies (brain MRI with gadolinium) and visual-evoked potentials will determine the presence of demyelination elsewhere in the CNS, indicating that the process is multifocal [4]. If the demyelination elsewhere is limited to the optic pathways, a diagnosis of neuromyelitis optica could be considered. The longitudinal extent of MRI lesions is possibly useful in determining the cause of TM, specifically in distinguishing between NMO spectrum disorders and MS in patients with idiopathic TM. In patients with APTM presence of any cerebral lesion increases the transition to MS by 60% and in presence of MS specific brain lesions the rate is 90% [6]. If widespread demyelination is seen beyond the optic nerve and tract, a diagnosis of either acute disseminated encephalomyelitis or MS should be considered [4]. Finally, individuals who have a single focus of demyelination in the spinal cord and who meet the criteria set forth above are defined as having ATM [7].

Clinical features, such as fever, rash, neck stiffness, immunocompromised state, genital infection, herpes zoster suggest an infectious etiology for ATM. In these cases, serum rapid plasma reagin and CSF studies (including CSF bacterial and viral cultures, CSF venereal disease research laboratory test, CSF viral polymerase chain reaction studies) should be obtained [9].

Other clinical features might be indicative of connective tissue diseases, such as SLE, Sjögren's syndrome, sarcoidosis, or mixed connective tissue disease. In these cases, the following serum studies should be considered: antinuclear antibodies, anti-double-strand DNA antibody, anti-cardiolipin antibody, lupus anticoagulant, angiotensin-converting enzyme level, SS-A (Ro), SS-B (La), B2-glycoprotein I, and complement levels [4]. A urinalysis for hematuria and proteinuria should also be obtained. Depending on the level of suspicion, other investigations such as lip/salivary gland biopsy, chest CT (with contrast), and Schirmer test should be considered. An algorithmic approach to acute transverse myelopathy is suggested in Fig. 4.3.

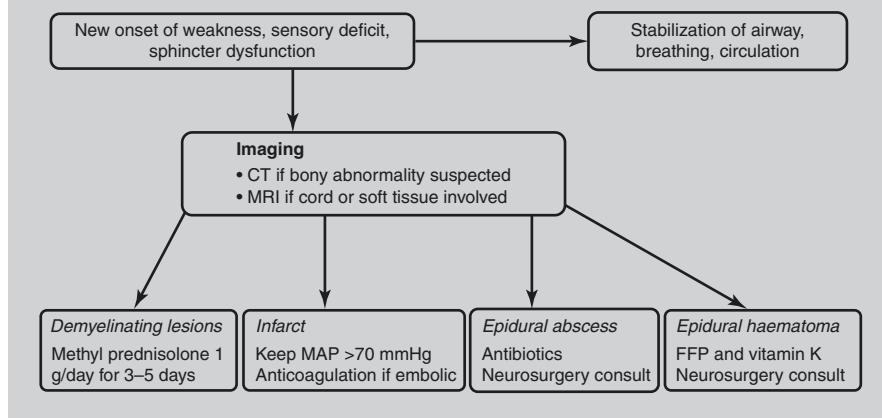
## Treatment

Successful treatment of ATM depends largely on rapid identification and treatment of the underlying etiology. Cases of idiopathic ATM are generally treated with



**Fig. 4.3** Algorithmic approach to acute transverse myelopathy

### Box 4.1 Management of Acute Spinal Cord Syndrome



steroids; methylprednisolone in a dose of 30 mg/kg is given for 3–5 days and then tapered. Plasma exchange therapy is considered for moderate-to-severe cases of ATM not responding to treatment with i.v. steroids (Box 4.1).

## Predictors of Recurrence

In adults the following parameters predicted increased the risk of recurrent TM, presence of MS specific brain lesions, female sex, CSF pleocytosis at onset of >5 white blood cells/mL, positive IgG index, positive oligoclonal band testing, vitamin D insufficiency and deficiency (25-OH vitamin D, 30 ng/mL and 20 ng/mL, respectively), ANA titer of 1:160, and presence of antibodies to Ro/SS-A antigen. In cases with high suspicion a repeat serology for ANA, antibodies to Ro/SS-A, and anti-aquaporin 4 antibody is suggested after 6–12 months [8]. In children relapses were more likely in girls and in patients with clinically silent brain lesions at the time of incident myelitis, presence of even, 1 clinically silent T2 bright brain lesion is a powerful predictor of MS [5].

## Multiple Sclerosis

Both progressive and relapsing multiple sclerosis are known to affect the spinal cord through inflammatory process. Progressive MS and malignant MS are known to affect multiple neurological systems in succession without recovery or with minimal recovery. Their diagnosis becomes obvious as they tend to produce symptoms, signs, and MRI lesions corresponding to various anatomical segments.

## Relapsing–Remitting Form of Spinal MS

This form of MS is the most common cause of an acute spontaneous spinal cord syndrome in patients between 15 and 50 years of age. Caucasians are at a higher risk of MS, with a much lower incidence in the black population and Asians. The incidence is also higher in females than in males.

## Risk Factors

Caucasian race and female gender confer a higher risk for MS. Genetic factors also seem to be involved. First-degree relatives of patients have a 2–5% risk of developing MS.

Most exacerbations of MS occur without any obvious preceding event. However, certain risk factors have been identified. Although the risk of MS exacerbation may drop dramatically during pregnancy, the 3–6 month post-partum is associated with an increased risk of exacerbation. Another risk factor for attacks is viral infections, especially those involving the upper respiratory tract. The association of MS attacks with stress is less clear.

## Clinical Features

In established multiple sclerosis (diagnosed using the revised McDonald criteria) when acute transverse myelitis appears, it is associated with later onset and optic neuritis [10]. Occurrence of ATM in MS patients shares many features with post-infectious myelitis. An important difference between the two is that the clinical manifestations of acute MS tend to evolve more slowly over a period of a few weeks. MS plaques mainly occur in the dorsal half of the spinal cord and involve the cervical and upper thoracic cord more commonly than the lower thoracic or lumbar areas. Plaques tend to occur bilaterally and symmetrically. Acute MS presents typically with numbness that spreads over one or both sides of the body with coincident asymmetrical weakness and then paralysis of the legs. As these deficits progress, the bladder is also commonly affected. The sensorimotor disturbance may extend to the arms and a sensory level can be demonstrated. As the majority of MS starts with a relapsing–remitting course, acquiring a history of relapses and remissions is essential. An MS attack is defined as a new symptom involving the nervous system, or the recrudescence of an old one, which lasts for >24 h and at intervals of 1 month. Occurrence of ATM as the initial presentation is rare. Only 0.7% of a Canadian population of 3500 people with MS had acute TM as their first attack. Those patients who present with ATM as clinically isolated syndrome (CIS) will be required to meet the 2010 revised McDonald criteria for the diagnosis of multiple sclerosis (Table 4.3).

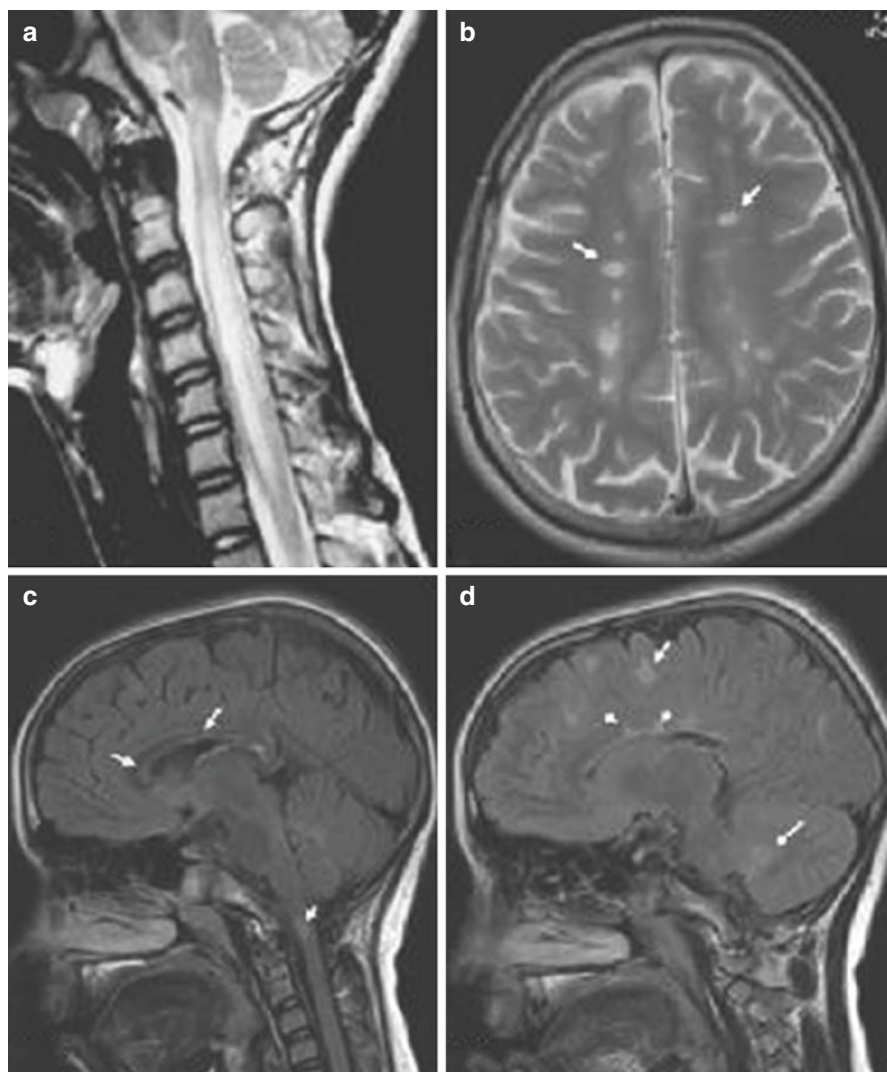
## Investigations

In a known case of MS, occurrence of a new spinal cord symptom poses no diagnostic problem. However, in 30–60% of cases, spinal cord symptoms are the first manifestation of the disease. In such cases it is essential to establish the existence of other silent lesions in the brainstem or optic nerves using MRI and brainstem auditory or visual-evoked potentials. MRI of the spine is initially done. The cord in MS cases shows localized swelling and edema with multifocal areas of abnormal signal on T<sub>2</sub>-weighted images (Fig. 4.4a). Contrast enhancement may be present.

A brain MRI is obtained to clarify if a case of myelitis represents an initial episode of MS. Periventricular, cortical or juxtacortical, infratentorial, optic nerve are

**Table 4.3** 2010 Revised McDonald criteria for diagnosis of multiple sclerosis

Clinical (attacks)	Lesions	Additional criteria to make diagnosis
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by <ul style="list-style-type: none"> <li>• <math>\geq 1</math> T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR</li> <li>• Await further clinical attack implicating a different CNS site</li> </ul>
1	Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by <ul style="list-style-type: none"> <li>• Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR</li> <li>• A new T2 and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing; OR</li> <li>• Await a second clinical attack</li> </ul>
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by <ul style="list-style-type: none"> <li>• <math>\geq 1</math> T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR</li> <li>• Await further clinical attack implicating a different CNS site AND dissemination in time, demonstrated by <ul style="list-style-type: none"> <li>– Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR</li> <li>– A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR</li> <li>– Await a second clinical attack</li> </ul> </li> </ul>
0 (progression from start)		One year of disease progression (retrospective or prospective) AND at least 2 out of 3 criteria: <ul style="list-style-type: none"> <li>• Dissemination in space in the brain based on <math>\geq 1</math> T2 lesion in periventricular, juxtacortical, or infratentorial regions</li> <li>• Dissemination in space in the spinal cord based on <math>\geq 2</math> T2 lesions; OR</li> <li>• Positive CSF</li> </ul>



**Fig. 4.4** (a) MRI cervical spine T<sub>2</sub> sagittal showing long segment of hyperintensity in the spinal cord, in a case of spinal MS. (b) MRI brain axial T<sub>2</sub>W image reveals discrete subcortical white matter hyperintense lesions (arrows). (c) MRI brain and cervical spine, sagittal section, FLAIR image reveals hyperintense lesions in the region of corpus callosum (large arrows) and upper cervical cord (small arrow). (d) MRI brain sagittal section, FLAIR image reveals hyperintensities in the subcortical white matter (arrows) and typically perpendicular to corpus callosum (Dawson fingers, arrow heads) and cerebellum (long arrow)

areas identified specific to MS in addition to spinal cord. A normal scan indicates that the risk of subsequent evolution to MS is low. On the other hand, the finding of multiple periventricular T<sub>2</sub> hyperintense lesions indicates a much higher risk of >50% for developing MS over the next 5 years (Figs 4.4b, c, d).

**Table 4.4** Recommended 2016 MAGNIMS MRI criteria to establish the dissemination in space in multiple sclerosis

Dissemination in space can be shown by involvement of at least two of five areas of the CNS as follows
• Three or more periventricular lesions
• One or more infratentorial lesion
• One or more spinal cord lesion
• One or more optic nerve lesion
• One or more cortical or juxtacortical lesion

2016 recommendations of MAGNIMS committee (Table 4.4) include the presence of the symptomatic spinal cord lesion for the lesion count [11] (note the 2010 MAGNIMS criteria exclude symptomatic brainstem/spinal cord lesion from the lesion count). Imaging of the whole cord, with at least two magnetic resonance sequences (e.g., T2 and short T1 inversion recovery, T2 and double inversion recovery, T2 and post-contrast T1 sequences), is preferable to increase confidence in lesion identification, in part because about 40% of spinal cord lesions are identified in the thoracolumbar region.

The CSF usually shows a mild lymphocytosis, but it is as often normal. Oligoclonal bands are variably present but their presence favors a likelihood of MS. CSF IgG synthesis is increased in MS compared to NMO and CSF matrix metalloproteinase-9 (MMP-9) was significantly higher in MS patients as compared to NMO [12].

**Treatment**

Clinical trials for the treatment of the spinal form of MS have not been satisfactory. Intravenous methylprednisolone in a dose of 500 mg–1 g is usually given for 3 days followed by oral prednisone 1 mg/kg/day for a period of ~2 weeks and then gradually tapered. Steroids have been shown to decrease time to maximal improvement but they do not increase the quality of recovery or modify the frequency or intensity of future attacks.

A Cochrane review compared methylprednisolone to ACTH in the management of acute exacerbations of MS [13]. Both interventions showed some protective effect against the neurological deficit getting worse in the initial weeks of treatment [13]. Another Cochrane review in 2009 found no differences in outcomes among patients taking oral or i.v. steroids for relapses [14]. This review was, however, limited by the small number of studies available for comparison. No long-term data are available to indicate whether steroids have any effect on long-term progression.

A course of plasma exchange may be tried for severe cases if steroids are ineffective.

**Prognosis**

Although nearly all MS deficits improve, the extent of improvement is variable. Sensory deficits resolve completely in about three-fourths of cases. Motor deficits

have a less favorable prognosis. Roughly half the patients with hemiparesis or monoparesis remit completely. The outlook is poorer in patients with paraparesis or quadriparesis. Only ~15% of patients with bladder involvement regain complete control.

Early relapses were associated with more rapid clinical course and frequent relapses in first 2 years were shown to associate with later disability.

MRI of the brain provides prognostic information in patients about their first attack of MS. Three or more lesions point to a 70–80% risk of developing MS in the next 10 years, whereas with a normal brain MRI, there is a <20% chance of developing MS within the next 10 years.

---

## Neuromyelitis Optica Spectrum Diseases

Neuromyelitis optica spectrum diseases (NMOSD), the syndrome of myelitis occurring with optic neuritis, has now been accepted a separate entity. Distinctive pathological features and a rapidly progressive clinical course, longitudinally extensive spinal cord lesions on MRI, a distinctive serum antibody (NMO-IgG) reacting with a water channel (antibody to aquaporin 4), and clinical response to immunosuppressive regimens appear to distinguish it from the spinal form of MS.

NMOSD comprises of both aquaporin 4 antibody positive and negative spectrum of neurological syndromes. The antibody positive spectrum ranges from pure neuromyelitis optica to overlap with systemic inflammatory diseases like Sjögren, SLE, and Behçet. The systemic diseases satisfy their respective diagnostic criteria most often. ATM as a presentation in these systemic inflammatory diseases is very rare.

NMO most commonly affects young adults, but has been reported in infancy through the ninth decade of life. The reported mean age of onset may be more than that for typical MS. The ratio of female:male patients is approximately 1.4–1.8. In western nations it is a rare disorder constituting ~1% of demyelinating illnesses. In contrast to MS, NMO appears to be more common in non-Caucasians, such as Asians, African-Americans, Japanese, and other Pacific islanders.

## Clinical Features

Transverse myelitis with bilateral spinal cord injury and neurological dysfunction worsening progressively over several hours to days and involving motor, sensory, and sphincter function is a characteristic presentation of this disease. Deep funicular or radicular pain, lower extremity paresthesia, or weakness may herald its onset. Weakness rapidly evolves to paraplegia or quadriplegia and is often associated with complete sensory loss caudal to the lesion and a flaccid bladder. The lesion usually extends over at least three contiguous segments of the spinal cord. Clinically, this may result in a state of “spinal shock” with flaccid weakness, absent tendon reflexes, and absent plantar responses. A small minority of patients experience incomplete



lesions that may present as hemicord or central cord syndromes. Lhermitte sign, tonic muscular spasms, and root pain may occur, especially in patients with relapsing disease.

Optic nerve involvement can be unilateral or bilateral. It is almost always sudden and severe with or without associated retro-orbital pain. Visual field defects are variable and take the form of central or paracentral scotomata and altitudinal or chiasmatic defects. Almost 40% of affected patients experience near-complete visual loss at some point during the first episode of optic neuritis in NMO. However, a majority of patients will experience some improvement in the visual deficits, particularly if their disease is monophasic. Accumulation of visual impairment is seen with successive episodes in relapsing patients.

## Investigations

MRI of the cord is characteristically abnormal showing areas of increased T<sub>2</sub> signal intensity across several sections of the cord. Swelling of the cord may also be seen. The optic nerves also show enhancement post-contrast. Lesions in area postrema, hypothalamus, brainstem, and optic nerve favor a diagnosis of NMOSD in an ATM [15]. The characteristic neuroimaging features of NMOSD are outlined in Table 4.5.

The CSF is frequently abnormal with slightly elevated protein levels and pleocytosis (including neutrophils). Presence of serum aquaporin 4 antibody is a highly specific biomarker for NMOSD. Aquaporin 4 antibodies are also known to occur in systemic inflammatory diseases such as SLE and Sjögren's syndrome. Additional investigations like ANA, anti-dsDNA, anti-Ro/SS-A are required along with other investigational searches to establish a diagnosis of these systemic diseases. A positive antibody in the above said panel can brand the disease as NMO overlap syndrome despite classical myelitis and optic neuritis picture.

Recently other biomarkers like antimyelin oligodendrocyte glycoprotein (anti-MOG), anti-NMDA type glutamate receptor are being increasingly investigated as alternative antibodies for aquaporin 4 antibody negative NMOSD [16].

The diagnostic criteria for NMOSD have been proposed by international consensus diagnostic criteria for neuromyelitis optica spectrum disorders (2015) (Table 4.4) [15].

In a patient presenting with ATM, progressive overall clinical course, atypical time to nadir (<4 h to >4 weeks), acute partial transverse myelitis, and CSF oligoclonal bands, atypical MRI features (<3 complete longitudinal segments, lesions located predominantly in the peripheral cord, and diffuse indistinct signal change) were all considered to predict a lesser likelihood of NMOSD [15].

## Treatment

An acute episode of NMO is treated with i.v. corticosteroids (500 mg–1 g of methylprednisolone) for 5 days.

**Table 4.5** Characteristic MRI features of NMOSD*Spinal cord MRI, acute*

- LETM lesion associated with acute TM
  - Increased signal on sagittal T2-weighted (standard T2-weighted, proton density, or STIR sequences) extending over 3 or more complete vertebral segments
  - Central cord predominance (more than 70% of the lesion residing within the central gray matter)
  - Gadolinium enhancement of the lesion on T1-weighted sequences (no specific distribution or pattern of enhancement is required)
- Other characteristic features that may be detected
  - Rostral extension of the lesion into the brainstem
  - Cord expansion/swelling
  - Decreased signal on T1-weighted sequences corresponding to region of increased T2-weighted signal

*Spinal cord MRI, chronic*

- Longitudinally extensive cord atrophy (sharply demarcated atrophy extending over 3 complete, contiguous vertebral segments and caudal to a particular segment of the spinal cord), with or without focal or diffuse T2 signal change involving the atrophic segment

*Optic nerve MRI*

- Unilateral or bilateral increased T2 signal or T1 gadolinium enhancement within optic nerve or optic chiasm; relatively long lesions (e.g., those extending more than half the distance from orbit to chiasm) and those involving the posterior aspects of the optic nerves or the chiasm are associated with NMO

*Cerebral MRI: NMOSD-typical brain lesion patterns (increased signal on T2-weighted MRI sequences unless otherwise noted)*

- Lesions involving the dorsal medulla (especially the area postrema), either small and localized, often bilateral, or contiguous with an upper cervical spinal cord lesion
- Periependymal surfaces of the fourth ventricle in the brainstem/cerebellum
- Lesions involving the hypothalamus, thalamus, or periependymal surfaces of the third ventricle
- Large, confluent, unilateral, or bilateral subcortical or deep white matter lesions
- Long (1/2 of the length of the corpus callosum or greater), diffuse, heterogeneous, or edematous corpus callosum lesions long corticospinal tract lesions, unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle
- Extensive periependymal brain lesions, often with gadolinium enhancement

Plasma exchange should be considered in severe cases and in patients unresponsive to steroids. Typically, about seven plasma exchanges are undertaken. Pain, spasticity, and sphincteric symptoms need to be treated. Muscle spasms usually respond to carbamazepine (100–200 mg b.i.d.). Patients with high cervical cord lesions may need ventilatory support.

## Prognosis

Attacks of NMO are usually severely disabling and the remissions are often incomplete. Disability tends to accumulate in a step-wise manner. Attacks of NMO are generally more severe than those seen in MS and disability progresses earlier. In a joint study published from UK and Japanese cohorts age and ethnicity were two

parameters that determined the prognosis. Younger onset was associated with more visual disability and older onset with motor disability. Older onset was also associated with increased mortality owing to the respiratory complications [17]. Another study comparing the prognosis of pediatric onset NMO with adult onset found diffuse inflammatory process on first brain MRI and to have a longer time to disability in pediatric patients than adult patients [18].

---

## Spinal Cord Vascular Syndromes

### Spinal Cord Infarction

Infarction of the spinal cord is uncommon compared with cerebral vascular events. The exact incidence of cord infarction is unclear. However, spinal cord infarcts account for ~1% of cases in most stroke series [19].

### Causes

Aortic disease is the commonest cause of spinal cord ischemia. Aortic surgery (especially for aortic aneurysms) is the leading cause [20]. This group comprises thoracic and abdominal aortic aneurysms, aortic dissection, aortic thrombosis, and rupture.

Asymptomatic aortic atherosclerosis can also cause spinal stroke [21]. Surgical risk is greater when surgery is complicated by intra-operative hypotension, time of aortic cross-clamping >30 to 45 min, or when the aorta is clamped proximal to the renal arteries [22]. Other etiological factors capable of decreasing blood flow through the anterior spinal artery are atlanto-occipital dislocation, cervical spondylosis, spinal trauma, and rarely sustained neck rotation. Vasculitis occurring in conditions such as SLE can also affect the spinal circulation. Rare iatrogenic causes of spinal artery ischemia include invasive procedures, such as thoracolumbar sympathectomy, vertebral arteriography, coeliac plexus block, lumbar epidural anesthesia, abdominal aortography, therapeutic renal artery embolization, and IABP (intra-aortic balloon pump counter pulsation) [22].

Spinal transient ischemic attacks (TIAs) are reversible focal neurological deficits that last for <24 h. Probable causes include emboli from the aorta, heart, or a vascular steal phenomenon involving a spinal AVM.

Venous infarctions of the cord are rare. The majority occur in patients with hypercoagulable states or vascular malformations. In Av malformations shunting of the arterial blood causes venous congestion, venous hypertension, venous infarction, and progressive myelopathy [23].

### Clinical Features

Spinal cord infarcts most commonly affect the thoracic segments of the cord. Several distinctive neurovascular syndromes can be seen. The most frequently seen

vascular syndrome of the cord is the anterior spinal artery syndrome, which involves the anterior two-thirds of the spinal cord. This syndrome is characterized by an abrupt onset of back pain followed by a rapidly progressive flaccid weakness below the level of the lesion. Analgesia and thermoanesthesia below the level of the lesion result from damage to the spinothalamic pathway. Dorsal column sensation is intact. Orthostatic hypotension may be seen in case of cord involvement above the origin of the greater splanchnic nerve at T4–T9 [24]. Impairment of bowel and bladder function occurs with complete suprasacral lesions. Lesions at or above the C3–C5 level may impair respiration.

The posterior spinal artery syndrome is less frequently seen and involves the posterior one-third of the cord. The patient presents with impaired vibration sense and proprioception below the level of the lesion because of involvement of the posterior columns. Involvement of the posterior horns at the level of the lesion can lead to global loss of sensation and loss of segmental reflexes [25] at that particular level.

Venous infarctions occur rarely. The most common presenting symptoms are back pain and lower limb weakness. Motor dysfunction in these cases progresses slowly. Hemorrhagic lesions tend to present with a sudden onset of severe pain in the back and legs followed by a progressive flaccid paraplegia. With non-hemorrhagic lesions, back pain is less marked and the evolution of symptoms is usually slower [26].

Spinal arteriovenous malformations are classified based on the schema provided by Spetzler et al. (Table 4.6). Spinal dural arteriovenous fistulas constitute more than 70% of spinal arteriovenous malformations (AVMs) and are mostly acquired [23].

Investigations

Imaging

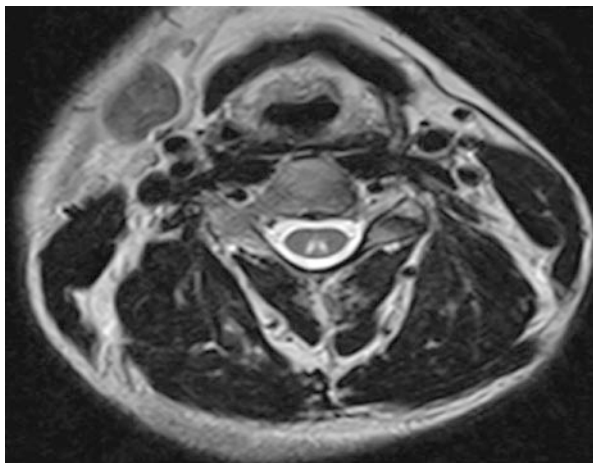
Imaging studies are the most important because they can identify or exclude space-occupying lesions that either compress the cord or compromise the circulation of the spinal cord.

The most helpful initial imaging study is a spinal MRI (Figs. 4.5 and 4.6). On MRI, the changes seen in the infarcted cord are similar to those seen in cerebral

Table 4.6 Spetzler classification of Spinal Arteriovenous malformations

<i>Arteriovenous fistulas</i>	
• Intradural	
– Dorsal	Radicular artery with medullar vein
– Ventral	Anterior spinal artery with coronal venous plexus
• Extradural	Radicular artery with epidural venous plexus
<i>AVMs</i>	
• Intramedullary	Glomus AVM with nidus in the cord
• Extradural–intradural	Juvenile AVM
• Conus medullaris nidus in the pia of the conus or cauda equina	

**Fig. 4.5** Anterior spinal artery infarct (T<sub>2</sub> axial)



**Fig. 4.6** Anterior spinal artery infarct (T<sub>2</sub> sagittal). Note the linear hyperintense intramedullary signal



infarcts [26]. The MRI in spinal cord infarction may be normal in the initial few hours or may show a high signal intensity on T<sub>2</sub>-weighted images. Enhancement of the infarcted tissue following contrast administration may be seen. In addition, MRI evidence of infarction of a vertebral body, especially in the absence of any epidural lesion, is highly suggestive of cord ischemia [27]. Diffusion-weighted imaging is

being used in recent years for the early diagnosis of cord ischemia. Restricted diffusion in the course of spinal cord ischemic infarction can be demonstrated using diffusion-weighted MRI (DW-MRI) [28].

In spinal AV malformations cord edema or ischemia manifests as longitudinally extensive hypertensive signal abnormality, sometimes up to the conus on T2-weighted FLAIR sequences throughout the central cord due to the effects of venous hypertension. Presence of hypointense rim surrounding a hyperintense signal represents deoxygenated hemoglobin in the dilated capillaries surrounding the edematous portions of the cord. Flow voids, usually located dorsal to the cord, represent dilated and tortuous perimedullary vessels belonging to the fistula. Three-dimensional phase-cycled fast imaging employing steady state acquisition (PC-FIESTA) and three-dimensional constructive interference steady state (CISS) can detect the vascular structures with more sensitivity. Absence of cord T2 hyperintensity and perimedullary flow predicts a low likelihood of spinal dural arteriovenous fistula [23]. MR angiography or digital subtraction angiography is indicated in patients with suspected vascular malformations. Chest radiography or CT may be considered in some patients to look for a suspected aortic dissection, aneurysm, or thrombosis (Fig. 4.7).

### Laboratory Studies

Investigations are directed towards the detection of possible underlying etiological factors, and especially include tests for vascular risk factors, such as diabetes mellitus, hypercholesterolemia, vasculitic disorders, and coagulopathies. Infectious causes, such as syphilis, herpes simplex, varicella zoster, HIV, and tuberculosis also need to be ruled out in selected cases.

### Treatment

In rare instances, the cause of infarction (e.g., vasculitis, aortic dissection) can be treated, but in most cases the only possible treatment is prophylactic and supportive.

*Specific:* Direct studies have not examined the efficacy of drug therapy in spinal cord infarction. Drug therapy is based on the consensus recommendation for treatment of stroke at any site. For patients with non-cardio embolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulants are recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, level of evidence 1) [29]. Aspirin (50–325 mg/day), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy (Class IIa, level of evidence 1) [28].

If ischemia is cardio embolic in origin, anticoagulant therapy is initiated. For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) atrial fibrillation (Class I, level of evidence 1), left ventricle thrombus (Class IIa, level of evidence 2), rheumatic valvular disease (Class IIa, level of evidence 3), and dilated cardiomyopathy (Class IIb, level of evidence 3), anticoagulation with

**Fig. 4.7** Spinal arteriovenous malformation with extensive flow voids in the cervical region



adjusted-dose warfarin (target INR 2.5; range 2.0–3.0) is recommended [29]. For patients who have modern mechanical prosthetic heart valves, oral anticoagulants are recommended, with an INR target of 3.0 (range 2.5–3.5) (Class I, level of evidence 2) [29].

Spinal AVMs need embolization or surgical resection. Prevention of recurrence also depends on adequate control of risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia.

## Supportive Measures

Prevention of complications is crucial. The vital signs should be carefully monitored and further hypotension avoided. Attention should also be paid to prevent bed sores, bladder and bowel care, deep vein thrombosis prophylaxis, and chest physiotherapy.

## Prognosis

Significant motor recovery in the first 24 h is a positive prognostic factor. Extensive deficits without initial improvement indicate a poorer prognosis [24].

---

## Surfers Myelopathy [30]

Surfers myelopathy is an acute myelopathy that develops immediately after surfing in a prone position on the surfboard for long periods.

## Clinical Features

It is characterized by lower back discomfort or pain that is followed 10–60 min later by acute urinary retention and progressive paraparesis.

## Investigations

MRI spinal cord shows hyperintense T2 signal and diffusion restriction from the mid- to lower-thoracic level to the conus medullaris.

## Mechanism

The possible causes were avulsion of perforating vessels, vasospasm of the artery of Adamkiewicz, or transient ischemia from tension on the spinal cord from hyperextension.

## Risk Factors

The proposed risk factors include a thin body habitus with underdeveloped musculature, dehydration, and a hypercoagulable state due to long-distance travel.

## Treatment

Spontaneous recovery is expected. No effective treatment postulated yet.



## Intraspinal Hemorrhage

Intraspinal hemorrhage can occur either in the subarachnoid space, the subdural space, or the epidural space. It can also occur within the substance of the cord (hematomyelia).

### Causes

The underlying cause is unknown in ~60% of cases. Roughly 25% of cases have coagulation defects. Approximately 5% of cases occur in patients with vascular malformations (intramedullary spinal AVM) and ~10% of cases can be attributed to trauma [3].

### Clinical Features

Patients usually present with a sudden onset of back pain, which is usually localized over the site of the lesion. There is a rapid onset of both sensory loss and motor weakness below the level of the hemorrhage. Bladder and bowel control is lost.

Subdural and subarachnoid hemorrhages have additional signs of headache and meningism.

### Investigations

The appearance of hematoma on imaging depends on several factors, such as the location, age, and state of oxygenation of the blood.

On MRI, blood is isodense to neural tissue in the hyperacute stage. Acute blood appears dark ( $T_2$  image). In the subacute stage the hematoma appears hyperintense on both  $T_1$ - and  $T_2$ -weighted images.

### Treatment

Intraspinal hematomas should be treated with surgical evacuation at the earliest. Bleeding tendencies including medical anticoagulation should be reversed with fresh frozen plasma (FFP) and/or vitamin K.

---

## Acute Myelopathy Associated with Infections

### Myelitis Associated with Viral Etiology [31]

#### Herpes Viruses

HSV 1 and HSV 2 viruses are known to involve the nervous system commonly. The involvement of spinal cord is more common in HSV 2 although case reports of

thoracic myelitis have been reported in HSV 1. These viruses are known for their dormancy in the dorsal root ganglion (trigeminal ganglion—HSV 1 and sacral dorsal root ganglia—HSV 2). HSV 2 can migrate retrograde up the cauda equina to the conus and lower spinal cord, causing a painful myeloradiculitis (Elsberg syndrome). Recurrent anogenital vesicular rash followed by pain or paresthesia in the distribution of the sacral sensory nerves and urinary retention is suggestive of HSV 2 infection.

### **Investigations**

CSF shows a lymphocytic pleocytosis, mildly elevated protein, normal glucose, and presence of HSV 2 DNA by PCR. MRI of the lumbosacral spine may show enlargement of the lower cord or enhancement of the lumbosacral nerve roots.

### **Treatment**

In immunocompromised patients is with 14–21 days of IV acyclovir 10 mg/kg. Adjunctive corticosteroid dosage regimen is 1 g of IV methylprednisolone daily over 3–5 days, followed with or without an oral taper.

### **Varicella-Zoster Virus**

Varicella-zoster virus (VZV) myelitis is more common than other herpes viruses.

VZV lies dormant in dorsal root ganglia and on reactivation travels along the sensory nerve to the surface, leading to a dermatomal rash. Concomitantly, retrograde travel to the CNS can result in myelitis (usually thoracic), meningitis, encephalitis, and even vasculitis.

### **Investigations**

MRI reveals T2 hyperintense lesion at the level of cord involvement (thoracic) with cord edema.

CSF shows a lymphocytic pleocytosis, mildly elevated protein, normal glucose, and VZV DNA can occasionally be detected by PCR. A diagnosis of VZV myelitis can be presumed in the setting of dermatomal rash with correlating myelopathy regardless of the CSF VZV serology or PCR.

### **Treatment**

IV acyclovir 10 mg/kg for 7–10 days and adjunctive corticosteroids.

### **Epstein–Barr Virus**

EBV infection is characterized by fatigue, splenomegaly, and pharyngitis. EBV can rarely be associated with intrinsic myelopathy and is usually combined with encephalopathy and radiculopathy. Most cases of myelopathy occur following acute infection. Rarely recurrence occurs. The presentations vary depending on the cord level involved, but, in general, symptoms and signs include spastic weakness, bladder retention, and a sensory level.

### **Investigations**

Detection of CSF EBV DNA in immunocompetent people can contribute to the diagnosis but can be falsely positive in Hodgkin's lymphoma and

immunocompromised state. Antibody detection is helpful in making the diagnosis as recent infection is evidenced by a heterophile antibody presence. Positive viral capsid antigen IgM and IgG and negative EBV nuclear antigen denote recent infection, although negative viral capsid antigen IgM may occur in some cases of recent infection.

### **Treatment**

EBV myelopathy has no definitive treatment as currently available antivirals are inadequate. Often, treatment is supportive with adjunctive corticosteroids.

### **Cytomegalovirus**

CMV infection is mostly asymptomatic in immunocompetent individuals. In immunosuppressed individuals (especially HIV infected) it affects multiple systems. In the spinal cord of the immune-suppressed patient, CMV can produce an ascending radiculomyelitis of the lumbosacral cord and cauda equina, sometimes also thoracolumbar myelitis. The clinical presentations are lower extremity weakness and bladder retention with or without progression.

### **Investigations**

The characteristic CSF profile is a neutrophilic pleocytosis with hypoglycorrhachia.

### **Treatment**

IV ganciclovir 5 mg/kg 12th hourly for 2–3 weeks oral valganciclovir 900 mg for 4 weeks along with HAART if HIV positive status.

Longitudinally extensive spinal cord lesions have been reported in dengue with variable response to steroids.

---

## **Myelopathy Associated with Bacterial Infection**

### **Spinal Epidural Abscess**

Infection is usually limited to the fatty tissue of the dorsal epidural space in between the ligamenta flava.

### **Causes**

In about one-third of cases the abscess is formed by contiguous extension of a local infection, such as a vertebral osteomyelitis [32]. In another third, hematogenous spread from a distant site (upper respiratory or urinary tract infection) [32] is responsible. Hematogenous spread is usually seen in intravenous drug abusers, immunosuppressed individuals, and patients with bacterial endocarditis [32]. In the remaining one-third of cases no clear source can be identified. *Staphylococcus aureus* is the organism implicated in more than half of the cases.

### **Clinical Features**

The thoracic and lumbar areas are most commonly involved, with cervical involvement being seen much less commonly. Initial symptoms are fever and pain over the site of the abscess. As the abscess enlarges it compresses the nerve roots producing radicular pain. Finally, either the spinal cord or the cauda equina is compressed resulting in motor and sensory loss below the level of compression. Symptoms tend to evolve gradually over days to weeks.

### **Investigations**

Peripheral blood usually shows leucocytosis; blood cultures should be done to look for the etiology and source of the infection.

Lumbar puncture should not be done as it might cause neurological deterioration. MRI shows both anatomical deformity and signal abnormality. When the source of infection is local, vertebral osteomyelitis or discitis can be seen. The disc margin becomes blurred and the disc loses height. The abscess is usually seen as an area of T<sub>1</sub> or T<sub>2</sub> signal prolongation showing peripheral contrast enhancement.

### **Treatment**

Treatment consists of a combination of systemic antibiotics and surgical decompression. Patients treated before neurological deficits develop usually recover completely. Broad-spectrum antibiotics, usually ceftriaxone and vancomycin, are used initially. Antibiotic coverage can later be modified according to the culture reports. Antibiotics are to be given for a minimum of 4 weeks.

When the infection is secondary to trauma or a neurosurgical procedure, an anti-staphylococcal penicillin, an aminoglycoside, and a third-generation cephalosporin are given in combination.

Decompression of the spinal cord with drainage of the abscess is the usual mode of surgical treatment. Because of the rarity of this condition, no randomized trials are available to guide treatment.

---

## **Myelopathy Associated with Intervertebral Disc Herniation**

Intervertebral disc herniation usually occurs dorsolaterally as the annulus fibrosus is reinforced in the midline by the posterior longitudinal ligament. The most common site of disc herniation is the lower lumbar region. This is believed to be due to thinning and weakening of the posterior longitudinal ligament as it extends caudally. Disc herniation may be sudden or gradual with the disc being slowly extruded through the annulus. In either case the herniated disc might compress the spinal cord or cauda equina. However, the cauda equina syndrome is only seen in ~1 to 16% of all lumbar disc prolapses. Disc herniation is a frequent cause of low back pain and usually affects adults in the age group of 25–45 years. The male and female genders are equally affected.

## Causes

Acute lumbar disc protrusion seen in young and middle-aged adults may be triggered by back strain and can be associated with a previous history of injury. In older patients the process is degenerative and the presentation is more likely to be gradual.

## Clinical Features

The patient presents with severe pain across the lower back. This is typically the case with a central disc protrusion at L4–L5 level, but a more lateral protrusion is classically accompanied by radicular pain radiating down one or both legs. The onset of pain may be sudden or gradual. It is usually sharp and is aggravated by standing, sitting, or moving, and is often relieved by rest and a recumbent position [33]. A central disc protrusion most commonly at L4–L5 may cause acute compression of the cauda equina. Usually, an extruded fragment of the disc affects all the roots of the cauda equina below the level of the lesion, giving rise to a lower motor neuron type of paraparesis with sphincter involvement [33]. Similarly, a lateral disc protrusion causing compression of the L5–S1 segment may produce an acute foot drop [33].

Scoliosis or a spasm of the erector spinae muscles may be seen on clinical examination. A positive straight leg raising test on examination indicates nerve root involvement. The test is positive if pain occurs when the leg is lifted between 30° and 70° above horizontal. Higher disc protrusion at about the L3–L4 level can be recognized by the femoral stretch test. Complete neurological examination of the lower limbs is mandatory. Perianal sensation should always be tested, as the cauda equina syndrome is associated with saddle anesthesia [33].

## Investigations

MRI is ideal, but the results have to be correlated with the clinical symptoms [34]. Plain films and CT scans are not as sensitive, but they help to evaluate for other skeletal causes of back pain.

## Treatment

NSAIDs are used for pain relief. Opioids can be used for short-term pain relief. Muscle relaxants are of limited benefit. Most acute attacks settle with conservative management.

Surgery—discectomy, microdiscectomy, or decompressive laminectomy—is indicated in a relatively small number of cases. Surgery is indicated in patients in whom no significant recovery is seen even after 6 weeks of conservative management, and in those with severe motor or sensory symptoms, as well as in patients with the cauda equina syndrome.

Trials comparing discectomy with conservative management have given suggestive rather than conclusive results. Surgical discectomy for carefully selected patients with sciatica caused by lumbar disc prolapse provides faster relief from pain compared with conservative management. However, uncertainty still exists about the effects of surgery on the lifetime natural history of the disease. Nevertheless, other trials show that discectomy produces better clinical outcomes than chemonucleolysis which, in turn, is better than placebo.

## Prognostic Factors

Patients with complete perineal anesthesia at presentation tend to have permanent paralysis of the bladder [35]. The prognosis for recovery of motor function is the same in both acute- and slower-onset disc disease. However, recovery of bladder function is usually less in the patients with a more acute onset [35].

---

## Heroin Myelopathy [36]

Acute myelopathy that develops in heroin users especially following abstinence.

## Clinical Features

Acute myelopathy along with acute renal failure, rhabdomyolysis, and liver failure. Paraplegia, urinary retention, and rhabdomyolysis are typical.

## Investigations

MRI may be normal early but later shows T2 hyperintensity over several spinal cord segments. CSF can be normal or show increased protein with or without pleocytosis.

## Mechanism

The pathophysiology is postulated to be a hypersensitivity/vasculitis mediated spinal injury.

## Treatment

Supportive. Role of steroids is debated. Recovery is variable. No prognostic factors identified.

## **Malignant Compression of the Spinal Cord**

Malignant spinal cord compression occurs in 5–10% of all patients with cancer. Metastatic involvement of the spine is the commonest form of skeletal involvement. Epidural tumor is the first manifestation of malignancy in ~10% of cancer patients. The thoracic spine is the most common site of malignant involvement (60%) followed by the lumbosacral (30%) and cervical spine (10%).

### **Causes**

Lung, prostate, and breast cancers most commonly metastasize to the spine. Myelomas, lymphomas, melanomas, genitourinary, and gastrointestinal cancers also often metastasize to the spine. Spinal cord compression develops when metastatic deposits to the vertebral body or pedicle enlarge and compress the underlying cord. Another cause of cord compression is the direct extension of paravertebral lesions through the intervertebral foramen. These cases usually involve hematological malignancies, such as lymphomas or myeloma. Parenchymal spinal cord metastasis due to hematogenous spread is a rare occurrence.

### **Clinical Features**

The most common initial symptom is localized back pain caused by involvement of the vertebrae by the tumor. Pain is usually present before other neurological deficits appear. Pain increases with movement, coughing or sneezing. It is more severe in the supine position. Radicular pain is less common and usually develops later in the course of the disease. Lhermitte sign may be present in case of cervical cord compression. Loss of bladder and bowel control may occur.

On examination, vertebral percussion helps to determine the level of vertebral compression. Neurological examination may reveal motor weakness, spasticity, and brisk reflexes. An extensor plantar is suggestive of significant compression. A sensory level with diminished posterior and spinothalamic sensation may be seen. Autonomic dysfunction presents with a distended bladder and diminished anal tone. Absent anal reflex and bulbocavernosus reflex confirms cord involvement.

### **Investigations**

Patients with cancer who develop back pain should be evaluated as soon as possible. In the presence of myelopathy on clinical examination, further investigation by MRI is essential. MRI visualizes vertebral involvement, epidural masses, intradural involvement, and cord compression. Vertebral collapse may be seen, but is not a reliable indicator of malignancy, as up to 20% of cases of vertebral collapse have benign causes, such as osteoporosis. However, MRI can be used to distinguish

between benign and malignant causes. Features that indicate malignant causes are hypointense marrow on T<sub>1</sub>-weighted images, marrow enhancement with intravenous contrast, >50% marrow involvement, and involvement of the posterior vertebral elements [37].

In patients with an unknown primary tumor, work-up includes chest imaging, mammography, an abdominal CT, and measurement of prostate-specific antigen.

## Treatment

Treatment is aimed at both relief of pain and preservation of neurological function.

Spinal immobilization precautions should be used in patients with neurological impairment. Corticosteroids have been found to decrease cord edema and transiently improve symptoms. An evidence-based guideline (1998) for emergency treatment of malignant spinal cord compression initially recommended high-dose dexamethasone—100 mg i.v. bolus, followed by 24 mg i.v. or orally every 6 h to promote post-treatment ambulation [38]. However, a more recent review concluded that the optimal dose of dexamethasone was not known [39]. Patients who are ambulatory do not need dexamethasone, but should be educated about the symptoms of malignant cord compression and started on dexamethasone if any symptoms arise before the end of radiotherapy.

Traditional indications for surgical intervention include an unknown etiology, failure of radiation therapy, radio-resistant tumor types (melanoma, renal cell carcinoma), pathological fracture dislocation, and rapidly evolving neurological symptoms [40]. A recent randomized study comparing surgical decompression followed by radiotherapy to radiotherapy alone has caused a major change in the approach to patients with malignant cord compression [40]. Outcomes are significantly better for patients treated surgically, with more ambulatory patients retaining ambulation (84% vs. 57%) and non-ambulatory patients regaining some muscle power (62% vs. 19%) [26]. Therefore, surgery should be considered in all patients with possible malignant cord compression and a combined approach with surgery and radiotherapy is indicated [39]. Standard doses of radiation range from 2500 cGy to 4000 cGy delivered in 10–20 fractions.

Patients who deteriorate neurologically even after radiotherapy could be considered for re-irradiation, as well as for surgery, especially if it has been more than 6 weeks since completion of their last course of radiotherapy.

Patients with extensive bony destruction should be considered for vertebral stabilization procedures before initiating radiotherapy.

Injection of acrylic cement is useful in patients with vertebral collapse.

## Prognosis

Rapid onset and progression of signs and symptoms are poor prognostic factors. Prognosis also depends on the primary tumor type.



## Radiation Spinal Cord Injury

Although most of the myelopathies associated with radiation injury are insidious onset acute transverse myelopathy following radiotherapy has been reported. This happens due to transient increase in spinal cord edema caused by disruption of the blood-spinal cord barrier that occurs during radiotherapy. It is responsive to steroid therapy [41].

---

## Paraneoplastic Myelopathy

This is a much rarer cause of myelopathy that is immune mediated compared with compressive myelopathy caused by metastasis in cancer patients. It is sometimes associated with paraneoplastic cerebellar dysfunction.

### Causes

It has been associated with ovarian carcinomas and lung carcinomas commonly. It is also seen in patients with lymphomas—both Hodgkin and non-Hodgkin.

### Clinical Features

The clinical syndrome consists of a rapidly progressive, painless loss of motor and then sensory tract functions, usually with sphincter disorder. Disability develops quickly and is generally severe. These changes can also be more chronic. Appearance of neurological symptoms and signs predates the cancer occurrence [41].

### Investigations

MRI demonstrates an area of T<sub>2</sub> signal change in the cord, or it may be normal. Symmetric, longitudinally extensive tract or gray matter-specific MRI changes are characteristic of paraneoplastic myelopathy [41]. Selective involvement of tracts is characteristic of paraneoplastic myelopathy. Biomarkers for paraneoplastic myelopathies have been identified. They can be classified into

1. Antibodies targeted against intracellular [41] (nuclear or cytoplasmic) neuronal elements—anti-Hu, anti-Yo, anti-Ri, anti-collapsin response mediator protein-5, anti-Ma, anti-amphiphysin antibodies.
2. Antibodies targeted against cell surface [41] (anti-NMDA receptor antibodies) that target neural plasma membrane ion and water channels, receptors, and synaptic proteins.

## Treatment

Treatment of the underlying malignancy. Steroids are ineffective against antibody targeted against intracellular element category but cell membrane antibody category responds well to antibody depleting therapy. Only a minority of patients improve with treatment [41].

---

## Tuberculous Spinal Osteomyelitis (Pott Disease)

Tuberculous osteitis of the spine, or Pott disease, is well known in regions of endemic tuberculosis. Children and young adults are frequently affected.

Bone and soft-tissue tuberculosis accounts for ~10% of extrapulmonary tuberculosis cases and between 1% and 2% of total cases. Tuberculous spondylitis is the most common manifestation of skeletal tuberculosis and accounts for 40–50% of all cases.

Pott disease most commonly involves the thoracic and lumbosacral spine. The region of the lower thoracic vertebrae is the most common area of involvement (40–50%), followed closely by the lumbar spine (35–45%).

## Causes

The osteomyelitis is usually the result of reactivation of tuberculosis at a site previously affected by hematogenous spread. An infectious endarteritis causes bony necrosis followed by the collapse of a thoracic or upper lumbar (less often cervical) vertebral body. This results in a highly characteristic angulated, kyphotic deformity.

A compressive myelopathy that results from the spinal deformity occurs in some cases, but it is surprisingly infrequent; an epidural tuberculous abscess is a more common cause of cord compression.

## Clinical Features

Back pain is the earliest and most frequent symptom. The pain caused by Pott disease can be spinal or radicular in nature. Constitutional symptoms include fever and weight loss. Neurological abnormalities occur in ~50% of cases and include spinal cord compression with paraplegia, impaired sensation, nerve root pain, or the cauda equina syndrome. Cervical spine tuberculosis is less common, but is potentially more serious because severe neurological complications are more likely. Patients with lower cervical spine disease can present with dysphagia or respiratory distress. Symptoms can also include torticollis and hoarseness of voice.

The clinical presentation of spinal tuberculosis in patients infected with the human immunodeficiency virus (HIV) is similar to that of patients who are

HIV-negative; however, spinal tuberculosis seems to be more common in the HIV-infected population.

On examination, almost all patients with Pott disease have some degree of spine deformity (mostly kyphosis). Large, cold abscesses may protrude under the inguinal ligament and may erode into the perineum or gluteal area.

## Investigations

Tuberculin skin test (purified protein derivative) results are positive in 84–95% of patients with Pott disease who are not infected with HIV.

The erythrocyte sedimentation rate may be markedly elevated ( $>100$  mm/h).

MRI is the most effective modality for demonstrating extension of the disease into the soft tissues and spread of tuberculous debris under the anterior and posterior longitudinal ligaments. MRI is also the most effective imaging study for demonstrating neural compression. MRI findings useful in differentiating tuberculous spondylitis from pyogenic spondylitis include a thin abscess wall with smooth enhancement.

Microbiological studies are used to confirm the diagnosis. Bone tissue or abscess samples are stained for acid-fast bacilli, and organisms are isolated for culture and susceptibility. PCR can be used to facilitate rapid diagnosis. CT-guided procedures can be used for percutaneous sampling of affected bone or soft-tissue structures. These findings are positive in ~50% of the cases. WHO has approved Gene-Xpert for diagnosis of extrapulmonary TB and rifampicin resistance and has suggested Gene-Xpert as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens [42].

## Treatment

Recommendations made in 2003 by the US Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Thoracic Society suggest that a four-drug regimen should be used empirically to treat Pott disease [43]. Isoniazid and rifampin should be administered during the whole course of therapy. Additional drugs are administered during the first 2 months of therapy. These are chosen from the first-line drugs, which include pyrazinamide, ethambutol, and streptomycin. The use of second-line drugs is indicated in cases of drug resistance. WHO guidelines 2010 recommend the following dosages for antituberculosis therapy [42].

Drug	Isoniazid (H)	Rifampin (R)	Pyrazinamide (Z)	Ethambutol (E)	Streptomycin (S)
Daily dose	10 mg/kg	10 mg/kg	35 mg/kg	30 mg/kg	15 mg/kg

The recommended duration is 2 months of intensive therapy with HRZE and 7 months of continuation therapy with HR. For treatment defaulted/relapses empirical MDR-TB regimen to be started and patient to be reviewed with a drug susceptibility test. If the drug resistance is not found, patient to be started on HRZES for 2 months, HRZE for 1 month followed by 5 months of HRE. If drug resistance found, individualized MDR-TB regimens to be decided [42].

Indications for surgical treatment of Pott disease generally include neurological deficit (acute neurological deterioration, paraparesis, and paraplegia), spinal deformity with instability, continuing progression of kyphosis, or the presence of a large paraspinal abscess; failed medical therapy and continued pain after medical therapy [44]. Common surgical approaches include anterior radical focal debridement and posterior stabilization with instrumentation.

---

## Decompression Sickness

### Causes

This myelopathy is observed in persons who are subjected to high underwater pressure and then ascend too rapidly. It affects mainly the upper thoracic spinal cord as a result of nitrogen bubbles that form and are then trapped in the spinal vessels. This produces ischemic lesions mainly in the white matter of the upper thoracic cord; also, the posterior columns are more affected than the lateral and anterior ones.

### Clinical Features

Symptoms occur almost immediately after resurfacing from a dive. Tract involvement is indicated by symptoms such as weakness, paresthesias, and bladder incontinence. The patient may also show partial improvement soon after. The patient may be left with residual involvement usually of the posterior tracts, causing spasticity and numbness. Acute abdomen like presentations have been reported along with neurological involvement in decompression sickness [45].

The mechanism suggested for the myelopathy in decompression sickness is accumulation of air bubbles in the epidural vertebral venous plexus of Batson. These air bubbles perpetuate a hemostatic plug and then lead to venous congestion and hypertension [46].

### Treatment

Immediate treatment consists of recompression in a hyperbaric chamber; later treatment is symptomatic, with antispasticity drugs and physical therapy. Recovery depends on time to recompression, later treatment leads to residual disability [47].

## Myelopathy with Normal MRI

An approach to patients presenting with acute transverse myelopathy with normal MRI [46] is given in Table 4.7.

**Table 4.7** Approach to myelopathy/myelopathy like presentations with normal MRI

Alternate examples	Explanations
Has a compressive cause been missed?	Epidural lipomatosis Dynamic compression on flexion extension only
Is it really a myelopathy?	<ul style="list-style-type: none"> <li>• Ganglionopathy, e.g., Sjögren, paraneoplastic, toxins</li> <li>• Peripheral nerve disease, e.g., acute inflammatory polyradiculoneuropathy</li> <li>• Plexopathy, e.g., neoplastic or idiopathic inflammatory</li> <li>• Neuromuscular junction, e.g., myasthenia gravis</li> <li>• Muscle, e.g., periodic paralysis</li> <li>• Motor neuronopathy, e.g., ALS/primary lateral sclerosis</li> </ul>
Is there a cerebral cause for the deficit?	Parasagittal meningioma Cerebral venous thrombosis Anterior cerebral artery thrombosis Normal pressure hydrocephalus Hydrocephalus Small vessel disease (vascular lower limb predominant parkinsonism) Other extrapyramidal disorders
Is it an acute presentation of an underlying chronic metabolic, degenerative, or infective myelopathy?	B <sub>12</sub> , folate, copper deficiency Nitrous oxide inhalation HTLV-1 HIV Syphilis Motor neuron disease (ALS) Adrenomyeloneuropathy Hereditary spastic paraplegia Friedreich's ataxia Lathyrism
Is the image quality adequate?	Motion artifact Low-strength magnet (0.5 T)
Were the images taken too early or too late in time and therefore "missed" the lesion (i.e., before it appeared or after it resolved)? Is the lesion too small to be seen on MRI? Is the weakness not organic ("functional")?	Long lesions of NMO may appear patchy or short, and hence nondiagnostic, if imaging is performed in the convalescent phase

## References

1. Gregory G, Jose B. Spinal cord anatomy, localization, and overview of spinal cord syndromes. *Continuum* (Minneapolis, Minn). 2008;14:11–35.
2. Adams RD, Victor M, Ropper AH. Principles of neurology. New York: McGraw-Hill; 2009.
3. Hauser SL, Ropper AH. Diseases of the spinal cord. In: Fauci AS, et al., editors. *Harrison's textbook of internal medicine*. 17th ed. New York: McGraw-Hill; 2008. p. 2588–95.
4. Barnes G, Benjamin S, Bowen JD, Transverse Myelitis Consortium Working Group, et al. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology*. 2002;59:500–5.
5. Banwell B, Dale RC. Understanding risk of relapse and risk of disability after childhood transverse myelitis. *Neurology*. 2015;84:332–4.
6. Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. 2011;77:2128–34.
7. Bruna J, Martínez-Yélamos S, Martínez-Yélamos A, et al. Idiopathic acute transverse myelitis: a clinical study and prognostic markers in 45 cases. *Mult Scler*. 2006;12:169–73.
8. Kimbrough DJ, Mealy MA, Alexandra Simpson RN, Michael Levy MS. Predictors of recurrence following an initial episode of transverse myelitis. *Neurol Neuroimmunol Neuroinflamm*. 2014;1:e4.
9. deSeze J, Stojkovic T, Breteau G, et al. Acute myelopathies: clinical, lab and outcome profiles in 79 cases. *Brain*. 2001;124:1509–21.
10. Scalfari A, Neuhaus A, Degenhardt A. The natural history of multiple sclerosis, a geographically based study: relapses and long-term disability. *Brain*. 2010;133:1914–29.
11. Filippi M, Rocca MA, Ciccarelli O. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol*. 2016;15:292–303.
12. Mandler RN, Dencoff JD, Midani F. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in cerebrospinal fluid differ in multiple sclerosis and Devic's neuromyelitis optica. *Brain*. 2001;124:493–8.
13. Filippini G, Brusaferri F, Sibley WA, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev*. 2000;4:CD001331. <https://doi.org/10.1002/14651858.CD001331>.
14. Burton JM, O'Connor PW, Hohol M, et al. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane Database Syst Rev*. 2009;3:CD006921. <https://doi.org/10.1002/14651858.CD006921.pub2>.
15. Wingerchuk DM, Banwell B, Bennett JL. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85:177–89.
16. Melamed E, Levy M, Waters PJ. Update on biomarkers in neuromyelitis optica. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e134.
17. Kitley J, Leite MI, Nakashima I. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain*. 2012;135:1834–184.
18. Collongues N, Marignier R, Ze'phir H, Papeix C. Long-term follow-up of neuromyelitis optica with a pediatric onset. *Neurology*. 2010;75:1084–8.
19. Sandson TA, Friedman TH. Spinal cord infarction: report of 8 cases and review of literature. *Medicine*. 1989;68:282–92.
20. Benavente O, Barnett HJM. Spinal cord ischaemia. In: Barnett HJM, Mohr JP, Stern BM, Yatsu FM, editors. *Stroke: pathophysiology, diagnosis and management*. 3rd ed. Philadelphia: Churchill Livingstone; 1998. p. 751–65.
21. Herrick MK, Mills PE Jr. Infarction of spinal cord: two cases of selective gray matter involvement secondary to asymptomatic aortic disease. *Arch Neurol*. 1971;24:228–41.

22. Szilagyi DE, Hageman JH, Smith RF, et al. Spinal cord damage in surgery of the abdominal aorta. *Surgery*. 1978;83:38–56.
23. Rabinstein AA. Vascular myelopathies. *Continuum (Minneapolis)*. 2015;21(1):67–83.
24. Cheshire WP, Santos CC, Massey EW, et al. Spinal cord infarction: etiology and outcome. *Neurology*. 1996;47:321–30.
25. Hughes JT, Brownell B. Spinal cord ischaemia due to arteriosclerosis. *Arch Neurol*. 1966;15:189–202.
26. Kim RC, Smith HR, Henbest ML, et al. Nonhemorrhagic venous infarction of the spinal cord. *Ann Neurol*. 1984;15:379–85.
27. Haddad MC, Aabed al-Thagafi MY, Djurberg H. MRI of spinal cord and vertebral body infarction. *Am J Neuroradiol*. 1992;13:145–54.
28. Kuker W, Weller M, Klose U. Diffusion-weighted MRI of spinal cord infarction—high resolution imaging and time course of diffusion abnormality. *J Neurol*. 2004;251:818–24.
29. Sacco RL, Adams R, Albers G, American Heart Association, American Stroke Association Council on Stroke, Council on Cardiovascular Radiology and Intervention, American Academy of Neurology, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:577–617.
30. Chang CWJ, Donovan DJ, Liem LK. Surfers' myelopathy. *Neurology*. 2012;79:2171–6.
31. Lyons JL. Myelopathy associated with microorganisms. *Continuum (Minneapolis)*. 2015;21(1):100–20.
32. Darouiche RO, Hamill RJ, Greenberg SB, et al. Bacterial spinal epidural abscess: review of 43 cases and literature survey. *Medicine*. 1992;71:369–85.
33. Gregory RO, Seto CK, Wortley GC, et al. Acute lumbar disc pain: navigating evaluation and treatment choices. *Am Fam Physician*. 2008;78:835–42.
34. Jarvik JG, Hollingworth W, Martin B, et al. Rapid MRI versus radiographs for patients with low back pain: a randomized controlled trial. *JAMA*. 2003;289:2810–8.
35. Kostuik JP, Harrington I, Alexander D, et al. Cauda equine syndrome and lumbar disc herniation. *J Bone Joint Surg Am*. 1986;68:386–91.
36. Goodman BP. Metabolic and toxic myelopathies. *Continuum (Minneapolis)*. 2015;21(1):427–40.
37. Tan DYL, Tsou IYY, Chee TSG. Differentiation of malignant vertebral collapse from osteoporotic and other benign causes using magnetic resonance imaging. *Ann Acad Med Singap*. 2002;31:8–14.
38. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol*. 1998;16:1613–24.
39. Loblaw DA, Lapierre N, Perry J, Members of the Neuro-Oncology Disease Site Group, et al. Malignant extradural spinal cord compression: diagnosis and management. Evidence summary report 9–9. Toronto: Cancer care Ontario; 2007.
40. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. *Lancet*. 2005;366:643–8.
41. Chamberlain MC. Neoplastic myelopathies. *Continuum (Minneapolis)*. 2015;21(1):132–45.
42. Mohapatra BN, Mohanty CB. Treatment of tuberculosis WHO guidelines 2010. [http://www.apiindia.org/pdf/medicine\\_update\\_2011/81\\_treatment\\_of\\_tuberculosis.pdf](http://www.apiindia.org/pdf/medicine_update_2011/81_treatment_of_tuberculosis.pdf)
43. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603–62.

44. Rasouli MR, Mirkoohi M, Vaccaro AR. Spinal tuberculosis: diagnosis and management. *Asian Spine J.* 2012;6(4):294–308.
45. Kannan B, Kannan A, Saravanan C, Venkatesan EP. First case report of caissons disease with pneumobilia. *Neurol India.* 2014;62:690–1.
46. Hallenbeck JM, Bove AA, Elliott DH. Mechanisms underlying spinal cord damage in decompression sickness. *Neurology.* 1975;25:308–316A.
47. Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. *Semin Neurol.* 2008;28(1):105–20.



# Neuromuscular Emergencies

# 5

Kavita Mohindra Grover and Naganand Sripathi

## Introduction

A conscious patient presenting to the emergency with sudden or relatively rapid onset of weakness should raise the suspicion of a disorder affecting the motor unit, in addition to the other parts of the neuraxis. The various neuromuscular disorders with such presentations can be categorized into disorders affecting the nerve roots, peripheral nerves, neuromuscular junction or the muscle (Table 5.1).

A rapid and systematic approach is mandatory for avoiding an incorrect diagnosis and unnecessary investigations. The following points are of extreme importance when evaluating such a patient.

1. ABC—Assess the integrity of the airway, breathing and circulation.
2. Support and stabilize the patient.
3. Obtain a focused history, including known history of neuromuscular or systemic disorder, medication list, exposure to toxins, travel, occupation, snake or tick bite, and dietary intake in the last few days prior to symptom onset.
4. Localize to a specific level of motor unit. (Refer to the text below for examination details for each disorder.)
5. Laboratory studies and electrodiagnostic testing, as applicable.
6. Treatment of the identified specific entity.

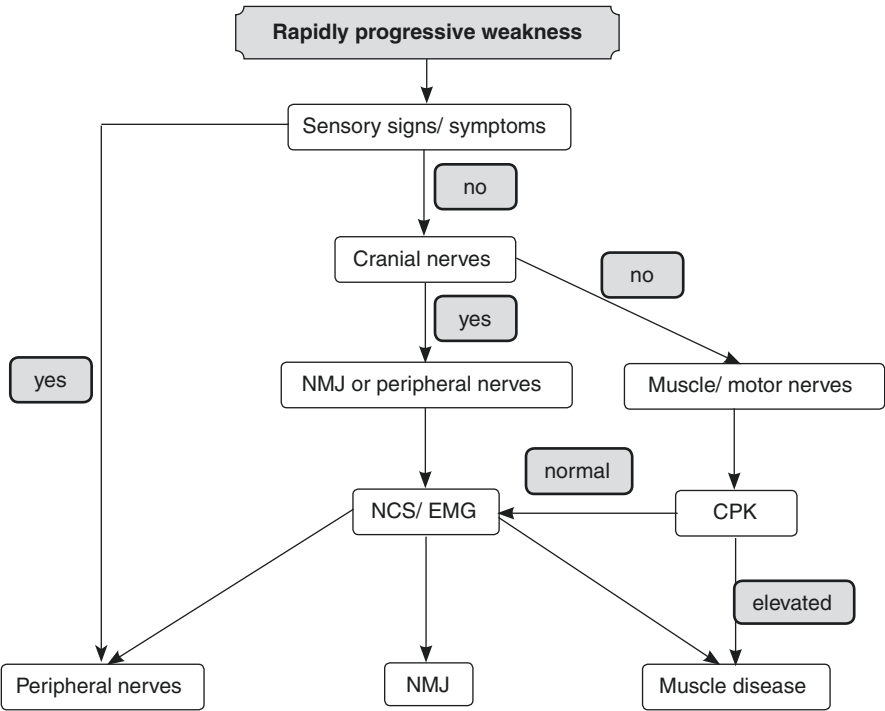
The approach to a patient presenting at the emergency department with rapidly progressive weakness that is suspected to be caused by a neuromuscular disorder is outlined in Fig. 5.1.

---

K. M. Grover (✉) · N. Sripathi  
Department of Neurology, Henry Ford Hospital and Wayne State University,  
Detroit, MI, USA  
e-mail: [nsripat2@hfhs.org](mailto:nsripat2@hfhs.org)

**Table 5.1** Disorders causing rapidly progressive weakness

Level of motor unit	Disorder
Nerve root/peripheral nerve	Guillain–Barré syndrome
	Tick paralysis
	Porphyric neuropathy
	Diphtheritic neuropathy
	Arsenic/thallium poisoning
	Shellfish poisoning
	Ethylene glycol poisoning
Neuromuscular junction (NMJ)	Myasthenia gravis
	Botulism
	Organophosphate poisoning
	Hypomagnesaemia
	Snake, spider and scorpion bites
Muscle	Periodic paralysis
	Rhabdomyolysis/myoglobinuria



**Fig. 5.1** Flow chart showing a schematic diagnostic approach to rapidly progressive weakness secondary to neuromuscular disorders. *NCS* nerve conduction studies; *EMG* electromyography, *CPK* creatine phosphokinase, *NMJ* neuromuscular junction

## Specific Disorders

### Guillain–Barré Syndrome (GBS)

The first report of this disorder dates back to 1859, when Landry published a report on 10 patients with ascending paralysis. Later, the main clinical features of this disease entity emphasized by Guillain, Barré and Strohl were motor weakness, paraesthesiae with slight sensory loss, areflexia and cerebrospinal fluid with albuminocytological dissociation.

#### Incidence and Prevalence

The incidence of GBS is 1–2/100,000/year, with a male to female ratio of 1.25:1. The peak occurrence is in young adults and in individuals over 55 years of age.

#### Causes

The exact cause for the occurrence of GBS is not known. Approximately two-thirds of the patients report a preceding infection (respiratory or gastrointestinal), immunization or surgery. *Campylobacter jejuni* is the most commonly encountered antecedent infection. It has been reported to cause predominantly motor weakness and is associated with a poorer outcome [1, 2]. Cytomegalovirus (CMV) affects younger patients, with greater sensory loss and cranial nerve involvement. CMV infection is reported in 11–20% of patients [3–5]. GBS with preceding CMV infection is associated with more severe disease, respiratory insufficiency and a longer median time to independent walking [6].

Other infections include those with mycoplasma, Epstein–Barr virus, human immunodeficiency virus (HIV) and hepatitis A. Implicated vaccines include those for tetanus, influenza, rabies, oral polio and swine flu. Several cases have been reported in immunocompromised patients with Hodgkin lymphoma and after solid organ or bone marrow transplantation [7–10].

#### Clinical Features

The presenting symptoms may vary from paraesthesiae, sensory symptoms with weakness or weakness alone. Paraesthesiae are the initial presentation in up to 50% of patients, eventually occurring in 70–90%.

A typical presentation includes symmetrical ascending weakness, initially affecting the lower extremities. Over a period of hours to days, the weakness ascends to the upper extremities, face and bulbar muscles. Approximately 30% of patients may progress to quadriplegia and another 30% may become bed-bound. A small percentage of patients may have descending weakness from the cranial nerves or arms to the legs.

Cranial nerve involvement is fairly common, occurring in up to 70% of patients. Bifacial weakness is seen in at least one-half of the patients. The extra-ocular muscles and tongue can also be affected, although not as commonly.

Sensory loss is not a prominent symptom; however, when present, it is often symmetrical and limited to the distal extremities. It typically affects all sensory modalities, although at times, may involve the vibration sensation only.

Most patients report moderate pain at the time of presentation. Pain may be described as dysaesthesias affecting the extremities or as diffuse myalgias and joint stiffness. Dysaesthesias may also be experienced by patients during the recovery phase.

Autonomic dysfunction has been observed in up to 65% of hospitalized patients. It may manifest as sympathetic dysfunction (orthostatic hypotension, anhidrosis, intermittent hypertensive episodes, sinus tachyarrhythmia, episodic sweating and acral vasoconstriction) or a parasympathetic dysfunction (urinary retention, gastrointestinal atony or iridoplegia, intermittent bradycardia, heart block and asystole). These spells can occur spontaneously or be triggered by tracheal suction, movement or positioning. The occurrence of respiratory failure requiring mechanical ventilatory support ranges from 12% to 23% in different studies [11, 12]. This may result from respiratory muscle weakness and/or aspiration of secretions.

Examination invariably shows weakness of the limb muscles, typically in an ascending fashion with the distal muscles being more severely affected. A progressive reduction of reflexes closely follows the pattern of weakness.

## Clinical Course

Typically patients experience maximum deficits within 4 weeks of symptom onset. Progression beyond a period of 4 weeks is classified as subacute (4–8 weeks) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), if beyond 8 weeks [13]. Fifty percent of patients reach the nadir of their clinical course in 2 weeks, 80% in 3 weeks and 90% in 1 month [14]. A few patients may have recurrent GBS (2–5%) [15].

## Differential Diagnosis

Many other disease entities can present with a subacute onset of motor weakness necessitating careful history-taking and neurological examination (Table 5.2). Another important category of disorders that should be kept in mind includes transverse myelitis or myelopathy and West Nile virus poliomyelitis.

## GBS Variants

Variations from the typical presentation described above have been recognized in the spectrum of this disorder (Table 5.3). The common features that suggest their link to GBS are history of a preceding illness/event, diminished reflexes, albuminocytological dissociation in the CSF and underlying immune-mediated aetiologies.

## Investigations

Although clinical history and examination are highly suggestive of this disorder in most patients, CSF examination and electrophysiological studies are important in establishing the diagnosis of GBS.

**Table 5.2** Differential diagnosis of GBS and treatment

Porphyric polyneuropathy	<ul style="list-style-type: none"> <li>• Weakness and pain (arms &gt; legs)</li> <li>• May be asymmetrical</li> <li>• Severe paraesthesias</li> <li>• Autonomic instability</li> <li>• Prior attacks of abdominal</li> <li>• Pain and psychiatric episodes</li> <li>• ↑ Urinary porphobilinogen and Delta-aminolevulinic acid</li> <li>• EMG discloses motor axonal neuropathy</li> </ul>	<ul style="list-style-type: none"> <li>• Admit to ICU</li> <li>• Monitor autonomic function closely</li> <li>• Administer glucose and intravenous</li> <li>• Haematinics</li> </ul>
Vasculitic neuropathy	<ul style="list-style-type: none"> <li>• Multiple asymmetric mono-neuropathies</li> <li>• Asymmetrical weakness sensory loss and pain</li> <li>• Usually in context of systemic vasculitis, but may be isolated to peripheral nervous system</li> <li>• ↑ ESR</li> </ul>	<ul style="list-style-type: none"> <li>• Admit to ward</li> <li>• Nerve/muscle biopsy to confirm diagnosis</li> <li>• Treat with corticosteroids ± cyclophosphamide</li> </ul>
Diphtheritic polyneuropathy	<ul style="list-style-type: none"> <li>• Cranial polyneuropathy with paralysis of pupillary accommodation ± respiratory muscle involvement (1–2 weeks after pharyngeal infection)</li> <li>• Generalized sensory &gt; motor</li> <li>• Polyneuropathy (8–12 weeks after infection)</li> <li>• Cardiomyopathy</li> <li>• CSF protein elevation and leucytosis</li> <li>• Throat culture positive for <i>C. diphtheriae</i></li> </ul>	<ul style="list-style-type: none"> <li>• Admit to ICU</li> <li>• Administer antitoxin</li> </ul>
Tick paralysis	<ul style="list-style-type: none"> <li>• May involve bulbar and respiratory muscles</li> </ul>	<ul style="list-style-type: none"> <li>• Search for and remove tick</li> <li>• Supportive treatment</li> </ul>
Arsenic neuropathy	<ul style="list-style-type: none"> <li>• Sensorimotor neuropathy</li> <li>• Encephalopathy, systemic symptoms and signs are frequent</li> <li>• Elevated urine arsenic levels</li> <li>• EMG usually shows axonal neuropathy but demyelinating neuropathy may be seen</li> </ul>	<ul style="list-style-type: none"> <li>• Admit to ward</li> <li>• Consider chelation therapy</li> </ul>
Hypophosphataemia	<ul style="list-style-type: none"> <li>• Paraesthesias followed by generalized weakness and areflexia</li> <li>• Cranial nerve weakness</li> <li>• Ventilatory insufficiency</li> <li>• Associated encephalopathy</li> <li>• Population at risk—receiving intravenous hyperalimentation</li> </ul>	<ul style="list-style-type: none"> <li>• Monitoring in ICU</li> <li>• Administration of intravenous phosphate</li> </ul>

ICU intensive care unit, ESR erythrocyte sedimentation rate, CSF cerebrospinal fluid

Adapted from Bella I, Chad DA. Neuromuscular disorders and acute respiratory failure. *Neurologic Clinic* 1998; 16: Issue 2

**Table 5.3** GBS variants

Miller Fisher variant (5%)	Triad of ophthalmoplegia, areflexia, ataxia
Acute dysautonomia	Autonomic failure and areflexia with preserved strength
AMAN	Similar clinical features as classical GBS, however, have axonal involvement of only motor nerves on NCV/EMG
AMSAN	Similar clinical features as classical GBS, however, have axonal involvement of motor and sensory nerves on NCV/EMG
Pharyngo–cervical–brachial variant	Bulbar along with neck and proximal arm weakness. Relative preservation of lower extremity strength with intact sensory modality examination

*AMAN* acute motor axonal neuropathy, *AMSAN* acute motor and sensory axonal neuropathy, *NCV/EMG* nerve conduction velocity/electromyography

### Spinal Fluid Analysis

The typical finding is that of albuminocytological dissociation. The protein levels may be normal in the first week; however, they are usually elevated in the subsequent weeks. The CSF protein may remain normal in approximately 10% of patients throughout the course of the illness. Cell count is normal in a majority of the patients. The presence of CSF pleocytosis (>50 cells/ml) should prompt testing for HIV infection, CMV myeloradiculitis, Lyme disease or lymphoma.

### Nerve Conduction Studies/Electromyography (NCS/EMG)

In the first few days of illness, the results from nerve conduction studies may be normal. Demyelination is the primary pathology in the majority of patients with GBS. The earliest electrodiagnostic changes, occurring within 1 week of symptom onset, include absent or impersistent F-waves and H-reflexes. These findings reflect proximal demyelination, i.e. occurring at the root level. Preserved sural with abnormal median sensory conduction may also be seen in early GBS. In the subsequent weeks, NCV shows evidence of segmental demyelination: prolonged distal latencies along with conduction blocks and temporal dispersion. Prolonged F-response latencies and conduction velocity slowing are the other hallmarks of this disease entity. These findings are seen in 50% of patients by week 2 and in 85% by week 3. Electrophysiological criteria for acute demyelinating neuropathy should be followed for establishing the diagnosis [16].

Reduced recruitment is the only finding seen on an initial needle EMG. Increased spontaneous activity with fibrillation potentials may appear after 2–4 weeks, reflecting secondary axonal degeneration.

### Serological Tests

These are of limited value for the various preceding infections.

Other laboratory tests may show mildly abnormal liver function (up to 10% of patients), hyponatraemia (related to syndrome of inappropriate antidiuretic hormone—SIADH), elevated CPK (3–4 times normal) [17] and elevated white blood cell count.

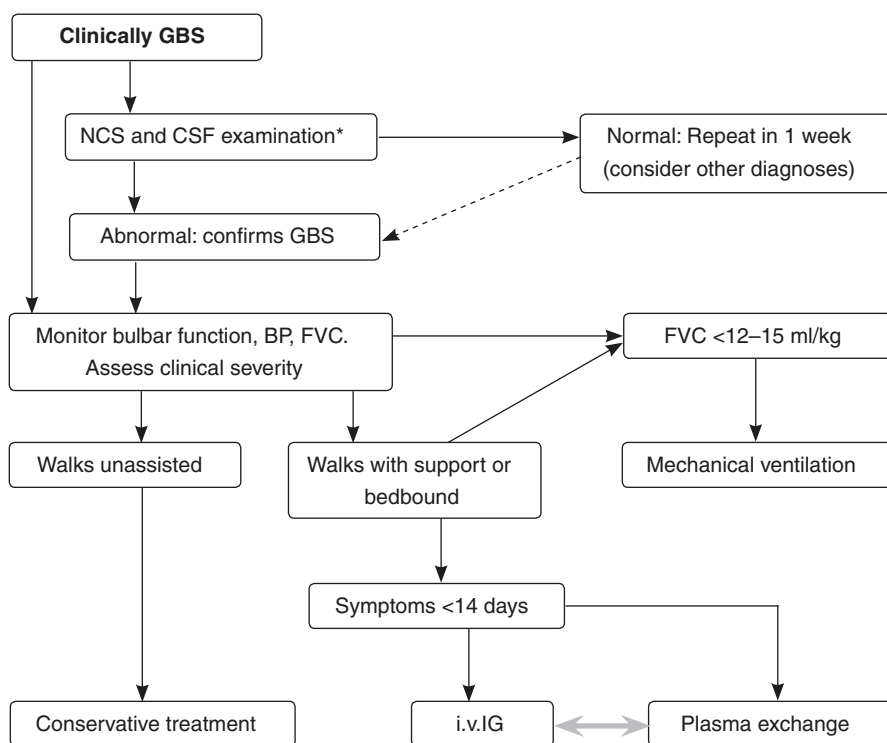
It is important to look for other mimics of GBS, and additional testing should be performed if any of those are suspected (please refer to Table 5.2 for specific testing methods).

In the case of a patient presenting with early urinary retention and a sharply demarcated sensory level suggesting spinal cord disease, spinal magnetic resonance imaging (MRI) of the appropriate level should be obtained before initiating any treatment.

## Therapy

The mainstay of treatment is immunomodulation with plasma exchange (PE) or intravenous immunoglobulin (i.v.IG) infusions [18, 19].

A flow chart for rapid assessment and management is outlined in Fig. 5.2. These immunomodulatory therapies are indicated in patients with severe and rapidly progressive weakness (inability to walk) or respiratory compromise. Ideally, it should be initiated within the first 2 weeks of the disease.



**Fig. 5.2** Flow chart showing an approach to the management of GBS. *Adapted from Bosch EP. Guillain-Barré syndrome: An update of acute immune-mediated polyradiculoneuropathies. The Neurologist 1998;4:211–26. \*A normal cerebrospinal fluid (CSF) and electrodiagnostic study do not exclude the diagnosis of Guillain-Barré syndrome (GBS). NCS nerve conduction study, CSF cerebrospinal fluid, BP blood pressure, FVC forced vital capacity, i.v.IG intravenous immunoglobulin*

### **i.v.IG**

The dosage regimen recommended is daily intravenous infusions of immunoglobulin (0.4 g/kg/day) for 5 days, to a total dosage of 2 g/kg [18].

Serum protein electrophoresis should ideally be done prior to administration of i.v.IG, to exclude IgA deficiency, as this can result in an anaphylactic reaction. This is, however not practical at times, given the cost involved and a low prevalence of IgA deficiency (approximately 1 in 1000). During therapy the patients need to be monitored for aseptic meningitis, renal impairment, congestive heart failure and thrombotic complications (stroke, myocardial infarction, venous thrombosis). In patients with hyperviscosity, congestive heart failure, chronic renal failure or IgA deficiency, plasma exchange should be preferred.

### **Plasma Exchange**

It is recommended that five single plasma volume exchanges (40–50 ml/kg) are given with a continuous flow machine on alternate days using saline and albumin as replacement fluid through a central venous catheter [19]. Continuous cardiac and haemodynamic monitoring needs to be done. In the absence of an arterial line, non-invasive blood pressure (BP) monitoring should be done every 15 min. Temperature should be monitored at least every hour along with strict monitoring of fluid balance throughout the procedure. Complications include venous access problems—haematoma at the puncture site, pneumothorax and catheter-related septicaemia. Plasma exchange is contraindicated in the presence of septicaemia, cardiovascular instability with hypotension or labile BP and active bleeding.

No treatment guidelines are available for the use of immunomodulatory therapy in patients who have been symptomatic for >14 days. Conservative management with cardiac and respiratory monitoring should be the mainstay in this group of patients.

Corticosteroids have been shown to be ineffective in most of the clinical trials [20, 21]. Further studies may be warranted to clarify this issue.

### **Respiratory Monitoring**

Initially, forced vital capacity (FVC) and negative inspiratory force (NIF) should be monitored every 4–6 h. Clinical parameters that predict the need for mechanical ventilation include rapid disease progression (symptom onset to admission <7 days), bulbar dysfunction, bifacial weakness and autonomic dysfunction [22].

Factors associated with progression to respiratory failure include vital capacity of <20 ml/kg, maximal inspiratory pressure of <30 cmH<sub>2</sub>O, maximal expiratory pressure <40 cmH<sub>2</sub>O (20–30–40 rule), or a reduction of >30% in vital capacity, maximal inspiratory pressure or maximal expiratory pressure [18] (Table 5.4).

Patients should be under observation in the intensive care unit (ICU) if the FVC is <1 l. Intubation should be electively done if FVC is less than 12–15 ml/kg or NIF is less than 25 cmH<sub>2</sub>O. Airway protection may also be required in case of excessive secretions.



**Table 5.4** Relationship between vital capacity, pathophysiology of lung function and suggested ventilatory therapy

Respiratory pathophysiology	Vital capacity	Ventilatory management
Poor cough, secretions accumulate	25–30 ml/kg	Chest physical therapy
Compromised sigh mechanism with atelectasis and hypoxaemia	20–25 ml/kg	Incentive spirometry to minimize atelectasis
	15–20 ml/kg	Elective intubation
Loss of sigh, atelectasis and shunting	10–15 ml/kg	Positive pressure ventilation
Hypoventilation, hypercapnia	5–10 ml/kg	Full ventilation

*Adapted from* Ropper AH. *Neurological and neurosurgical intensive care*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004

**Table 5.5** Negative prognostic indicators in patients with GBS [23, 24]

1. Older age (>60 years)
2. Rapid development of severe weakness (<7 days) with need for ventilatory support
3. Complete areflexia in the acute stage
4. Lack of treatment with plasma exchange or intravenous immunoglobulin (i.v.IG)
5. Longer time to improvement <ul style="list-style-type: none"> <li>• Initial improvement &gt;21 days</li> <li>• Disability present at 12–18 months</li> </ul>
6. Electrophysiological evidence of axonal loss as low compound motor action potential (CMAP) amplitudes <20% of normal, and lack of demyelinating features
7. Serological evidence of preceding <i>Campylobacter jejuni</i> infection or recent cytomegalovirus (CMV) infection

Continuous electrocardiogram (ECG) and BP monitoring should be done in patients with suspected autonomic dysfunction. Antihypertensive and vasoactive medications should be used with extreme caution.

Severe neuropathic pain may warrant treatment with tricyclic antidepressants, gabapentin or other medications. Musculoskeletal pain may respond well to the use of non-steroidal anti-inflammatory medications.

Prophylaxis for deep vein thrombosis is needed with subcutaneous unfractionated heparin or low-molecular-weight heparin, along with calf compression devices to prevent venous thrombosis and its complications.

Chest physiotherapy, physical and occupational therapy and nutritional support are of paramount importance in preventing complications and improving outcome.

## Prognosis

Certain historical, clinical and/or electrophysiological features can be used for prognostication. Factors predictive of a greater residual disability are listed in Table 5.5. Most patients recover functionally; however, up to 20% have some residual motor deficits 1 year later. Autonomic dysfunction usually improves in parallel with motor and sensory function. Residual long-term autonomic dysfunction is rare. Death occurs in 3–10% of patients and is related to pneumonia, medication-induced hypotension and autonomic dysfunction.

Myasthenia Gravis with Crisis (MG)

MG is an autoimmune disorder affecting the neuromuscular junction, with antibodies against acetylcholine (ACh) nicotinic post-synaptic receptors. The patients usually present with fatigable weakness variably affecting the ocular, bulbar or appendicular musculature.

Myasthenic crisis (MC) has been defined as an exacerbation of MG that leads to acute inability to swallow or difficulty in breathing, necessitating mechanical ventilation. The majority of patients developing MC have an identifiable precipitating factor. Occasionally, respiratory failure may be the presenting manifestation of MG.

Incidence and Prevalence

MG is a relatively rare neuromuscular disorder with a prevalence of 5–15/100,000 population. The incidence of MG is 3–4 per million per year. Approximately 15–20% of MG patients experience MC. This usually occurs in the first 2 years after the diagnosis in 74% of patients [25]. The incidence of thymoma is two times higher in MG patients with MC than in MG patients without a history of MC. Muscle-specific tyrosine kinase (MuSK) antibody-related MG also shows an increased incidence of MC [26].

The age of onset has a bimodal peak, with an earlier onset (second and third decade), being more common in women, and a later age of onset (sixth and seventh decades) seen equally in men and women.

Causes

The majority of the patients (80–85%) with MG have antibodies directed against ACh receptors on the motor endplate. Of the receptor antibody-negative patients, approximately 20% have antibodies against MuSK [26].

MC is commonly precipitated by infections, as many of the patients are immunosuppressed [27]. Several other causes can be identified with careful history-taking (Table 5.6). Several medications can trigger MC, including antibiotics, antihypertensives, high-dose corticosteroids and neuromuscular blocking agents (Table 5.7). A full list of medications can be found at [http://www.myasthenia.org/docs/MGFA\\_MedicationsandMG.pdf](http://www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf).

Table 5.6 Precipitating factors for myasthenic crisis

Infections (40%)
Medications
Stress
Surgery
Trauma
Fever
Pregnancy
Idiopathic (30%)

Modified from Bershad EM, Feen ES, Suarez JJ. Myasthenia gravis crisis. *South Med J* 2008; 101: 63–9 [28]

**Table 5.7** Drugs that exacerbate myasthenia gravis

Class	Drug
Immunosuppressants	High-dose corticosteroids (at onset of treatment)
Antibiotics	Aminoglycosides, fluoroquinolones, clindamycin, macrolides
Antiarrhythmics	Lidocaine, procainamide, quinidine
Antihypertensives	$\beta$ -blockers, calcium-channel blockers
Neuromuscular blocking agents	Botulinum toxin, curare derivatives, succinylcholine
Neuropsychiatric agents	Lithium, phenothiazines, phenytoin, trimethadione
Antirheumatic drugs	D-penicillamine, chloroquine
Others	Magnesium, lactate, iodinated contrast agents, citrate anticoagulant, diphenhydramine, emetine

*Modified from* Bershad EM, Feen ES, Suarez JI. Myasthenia gravis crisis. *South Med J* 2008; 101: 63–9 [28]

**Table 5.8** Consequences of weakness of the respiratory muscles

Diaphragmatic weakness	Orthopnoea, paradoxical breathing, reduced vital capacity, total lung capacity and maximal inspiratory pressure
Chest wall muscle weakness (inspiratory weakness)	Loss of sigh, which is required to maintain peripheral alveolar patency
Abdominal muscle weakness (expiratory weakness)	Reduced maximal expiratory pressure, reduced cough
Upper airway muscle weakness (mouth, uvula, palate, tongue and larynx)	Upper airway obstruction, inability to clear secretions, impaired swallowing, tendency to aspirate

*Adapted from* MacDuff A, Grant AS. Critical care management of neuromuscular disease, including long-term ventilation. *Curr Opin Crit Care* 2003; 9: 106–12 [29]

## Clinical Features

The manifestations of MC may be varied. In a patient with an established diagnosis of MG, worsening of myasthenia causes swallowing difficulty, as well as facial, masticatory and respiratory muscle weakness, making the patients prone to developing aspiration pneumonia. In others, MC may develop suddenly. A high index of suspicion is needed as MC may be a presenting manifestation of MG. MG presenting with crisis should be suspected in any patient with unexplained respiratory failure or requiring prolonged ventilation.

Weakness of the muscles of respiration leads to a cascade of events resulting in respiratory failure (Table 5.8).

An impending respiratory failure includes the following clues:

1. A gurgling dysarthric speech and stridor means poor airway protection.
2. The patient may appear anxious. Rapid and shallow breathing indicates respiratory muscle fatigue.
3. The presence of neck muscle weakness correlates well with diaphragmatic weakness.

4. Diaphragmatic weakness causes paradoxical chest movements (inward movement of abdomen during inspiration).
5. A reduced vital capacity <1000 ml is indicative of respiratory crisis. Close bedside pulmonary function tests every 4–6 h are required. In the presence of facial weakness, this measurement may not be entirely reliable. Single breath count is a simple bedside test for measuring the FVC. The number reached by the patient after a single breath multiplied by 100 roughly approximates the FVC. For example, a count of 20 equals 2000 ml.
6. Mechanical ventilation is indicated in MG patients with FVC <15 ml/kg (normal >60 ml/kg), NIF <–20 cmH<sub>2</sub>O (normal >–70 cmH<sub>2</sub>O) and peak expiratory flow (PEF) <40 cmH<sub>2</sub>O (normal >100 cmH<sub>2</sub>O).
7. Immediate intubation is necessary if the PaO<sub>2</sub> is <60 mmHg or PaCO<sub>2</sub> is >60 mmHg.

### Investigations

1. Close monitoring of patients with impending crisis requires bedside pulmonary function testing every 4–6 h. Most of the patients have orofacial weakness and may have difficulty in holding the mouthpiece securely.
2. Hypercarbia may be seen before hypoxia on arterial blood gas estimation.
3. Electrolytes, liver function tests, complete blood cell count with differential, chest X-ray for evaluation of pneumonia, urine analysis with culture and sensitivity, and blood cultures should be ordered to identify any underlying infection.
4. Edrophonium or neostigmine testing in naive patients with no previous diagnosis of MG should be done to establish the diagnosis. However, this should be performed in a monitored set-up.
5. Electrodiagnostic studies (repetitive nerve stimulation, NCV, EMG) should be performed in patients presenting for the first time to aid in diagnosis.
6. ACh receptor antibodies (if MC is the first presentation of MG, or in patients in whom MG is suspected) and anti-striated muscle antibodies (elderly MG patients, in patients with suspected thymoma) can be tested for. All three types of ACh receptor antibodies (binding, blocking and modulating) should be tested for a more definitive diagnosis. Testing for MuSK antibodies should be ordered if all the above antibodies are negative. Recently, the presence of potassium-channel antibodies has been described in patients with severe MC, along with myocarditis and myositis [30].
7. Thyroid-stimulating hormone (TSH) and connective tissue screening should be done (for evaluation of co-morbid conditions associated with MG, which can also exacerbate symptoms).
8. Chest computed tomography should be done to look for the presence of thymoma or to identify the cause of respiratory failure.
9. Edrophonium testing to distinguish MC from cholinergic crisis is discouraged by some authors [31] for the known cardiac side-effects, especially in elderly patients. However, this should be undertaken as per the clinician's discretion.

## Therapy

### Supportive Treatment

#### General Principles

It is of paramount importance to identify and treat the precipitating factors. Diagnostic work-up as listed above may assist in identifying the trigger, which requires additional treatment.

Several antibiotics interfere with neuromuscular transmission (Table 5.7), and empirical antibiotic use is not recommended. All steps should be taken to prevent pneumonia associated with assisted ventilation. Cardiac arrhythmias have been described in almost 17% of patients with MC [27]. Most of the arrhythmias may be benign, but fatal arrhythmias, including ventricular tachycardias and asystole, have also been reported [32].

Placement of the patient at 45° and avoiding gastric distension prevents aspiration pneumonia. A twice daily oral rinse with 15 ml of 0.12% chlorhexidine for 30 seconds reduces oral bacterial colonization [28]. Timely extubation based on the following parameters—FVC >15 ml/kg, NIF >−30 cmH<sub>2</sub>O, PEF >40 cmH<sub>2</sub>O, RSBI (rapid shallow breathing index: Tidal volume/respiratory rate) of >100—prevents complications from mechanical ventilation.

Daily assessments of these pulmonary function tests, along with adequate oxygenation, an intact respiratory drive and cough reflex, are all important measures in day-to-day management. Tracheostomy should be considered in all patients who are on mechanical ventilation for more than 2 weeks. Gastrostomy may also be required for adequate nutrition if the duration of the crisis is unduly long.

#### Mechanical Ventilation

Elective intubation is better and one should be alert and quick to make this decision. A rapid sequence oral intubation is preferred, and the patient should receive bag-masking to achieve an arterial saturation of >97%. Neuromuscular blocking agents should be avoided and, if necessary, vecuronium is the preferred agent. A commonly used anaesthetic agent is etomidate at a bolus of 0.2–0.3 mg/kg.

An optimal ventilator setting should be chosen to combat fatigue and promote lung expansion. This can be done by selecting assist control with PEEP (positive end-expiratory pressure) of 5 cmH<sub>2</sub>O. To avoid lung injury, lower tidal volumes at 6 ml/kg and faster rates of 12–16 breaths per minute may be selected [33].

### Acute Medical Treatment

Conclusive evidence to support whether plasma exchange or i.v.IG is more efficacious in the acute management of MC is lacking. Most of the experience is based on several small studies. Gajdos did not detect a clear difference between these modalities in a randomized clinical study [34]. Qureshi found better short-term improvement with PE, although it was with greater morbidity [35]. A therapeutic benefit has been observed in about 5 days with i.v.IG. In a recent literature review, plasma exchange was recommended as the primary modality of treatment [36].

### Plasma Exchange

Five single to 1.5 times plasma volume exchanges (40–50 ml/kg) with a continuous flow machine on alternate days using saline and albumin as replacement fluids are recommended.

### i.v.IG

The dosage regimen recommended is daily infusions of immunoglobulin (0.4 g/kg/day) for 5 days, reaching a total dosage of 2 g/kg.

### Corticosteroids

It is well known that initiation of corticosteroid therapy is associated with transient worsening of myasthenia. However, when the patient is being monitored in the ICU and maintained with adequate ventilation, use of high-dose corticosteroids is relatively safe. A slower incremental increase may also be used if the clinician is concerned about worsening. Steroids should always be instituted unless otherwise contraindicated. The recommended dose of prednisone is 60–100 mg given daily until improvement in the symptoms is noted—85% of patients improve in 3 weeks, and 100% respond in 2 months [37].

Acetylcholinesterase inhibitors are not required as an acute therapy, as they promote excessive secretions leading to respiratory complications and cardiac arrhythmias.

Another important aspect is the cholinergic crisis with excessive medications. There are no randomized, controlled studies for definite recommendations regarding acetylcholinesterase inhibitor usage during MC. In a recent series, no significant difference was noted in the short-term efficacy, long-term outcome and side-effects among the three groups (pyridostigmine, pyridostigmine and prednisone, and PE) [27]. However, it is recommended to discontinue cholinesterase inhibitors throughout the period of ventilation, and especially in the setting of planned thymectomy or extubation [38, 39]. Long-term therapies for MG must be instituted once the crisis is under control.

### Prognosis

MC typically lasts for an average of 2 weeks. Independent predictors of prolonged mechanical ventilation include.

1. Age >50 years
2. Pre-intubation bicarbonate >30 mg/dl
3. Peak vital capacity <25 ml/kg on days 1–6 post-intubation [25].

Failure to extubate or wean away from the ventilator occurs with increased frequency in patients with MC (approximately 44%). Factors observed with failure to wean or extubate are male sex, atelectasis, prior history of MC and prolonged intubation (>10 days) [40].

The mortality rate of MC is 4–5%. Increased access to treatment and improved respiratory management in ICUs with elective intubation and better antibiotics has contributed to a better prognosis than before.

## Botulism

It is caused by botulinum toxin, which is produced by the bacterium *Clostridium botulinum*.

### Clinical Features

This entity may present with a rapid onset of weakness along with bulbar dysfunction and respiratory failure. The toxin causes blockade of release of ACh at the pre-synaptic level, which results in clinical weakness.

### Diagnosis

This is established by obtaining a history of an infected wound, consumption of contaminated or spoiled food, demonstration of an incremental response (>100%) on rapid frequency (50 Hz), repetitive nerve stimulation test, and isolation of toxin on analysis of the serum, faeces or implicated food.

### Treatment

This encompasses supportive care with mechanical ventilatory support and wound debridement. Botulinum antitoxin is of benefit when used within the first 24 h.

## Snake Envenomation

Snakebites are a common cause of mortality in the tropics, with an estimated death rate of 35,000–50,000 per year [41]. Snake venom contains different enzymatic and non-enzymatic components that are loosely categorized as neurotoxins and haemorrhages.

### Clinical Features

Snake envenomation causes the following assortment of clinical manifestations: Procoagulant activity causing consumptive coagulopathy leading to systemic haemorrhages, renal failure due to acute tubular necrosis, local cellulitis and gangrene, and finally a myasthenic syndrome.

Snakebites of the elapid group (cobras and kraits) are predominantly neurotoxic [41, 42]. Neuromuscular toxicity results from a blockade of both pre- and post-synaptic neuromuscular transmission. Neuromuscular blockade with cobra venom is predominantly post-synaptic and that of krait venom is pre-synaptic. Neurotoxicity results in a completely reversible muscle paralysis. The weakness mimics a myasthenic syndrome with clinical manifestations that include ptosis, fatigability, external ophthalmoplegia and weakness of the masticatory, facial, palatal, neck flexor and proximal muscles. The weakness may progress to respiratory failure.

### Diagnosis

Sensory examination is normal with preserved deep tendon reflexes. The edrophonium test is negative, which distinguishes this disorder from MG. High-frequency repetitive nerve stimulation at 50 Hz produces a decremental response [42].

## Treatment

These patients require supportive care with ventilatory assistance, polyvalent anti-snake venom (ASV) and anticholinesterase medications. There is no consensus regarding either a loading or maintenance dose of ASV. Agarwal et al. [41] in a recent study did not notice a difference between the high-dose (100 ml of ASV at presentation followed by 100 ml every 6 h until recovery) and low-dose (100 ml ASV as a loading dose followed by 50 ml 6 h later) groups. The same group felt that administration of neostigmine or other cholinesterase inhibitors is not of any benefit [41]. However, other authors feel that anticholinesterase treatment is the cornerstone of treatment [43, 44].

## Organophosphate Poisoning

Organophosphates (OPs) have been used as insecticides for over 50 years. As a group, they are potent cholinesterase inhibitors causing severe toxicity following ingestion, inhalation or topical exposure. More than 3 million people worldwide are exposed to organophosphates and carbamates per year with an estimated fatality of 300,000 [45, 46].

The common agents used as insecticides are parathion, fenthion, malathion, diazinon and dursban. These agents bind and inhibit red blood cell acetylcholinesterase (also called neutral acetylcholinesterase). This causes synaptic abundance of acetylcholine. OPs also inhibit plasma cholinesterase (pseudo-cholinesterase or butyl cholinesterase) and neuropathy target esterase.

The route of absorption, lipid solubility and pharmacokinetics of individual agents determine the onset and duration of the toxicity.

## Clinical Features

The common features of toxicity are outlined in Table 5.9.

The degree of toxicity may be measured by RBC acetylcholinesterase activity (Michel's method, range  $0.74 \pm 0.06$  delta pH units/h) [49]. Plasma cholinesterase does not correlate well with severity of poisoning. In doubtful cases, a trial of 1 mg of atropine in adults or 0.01–0.02 mg/kg in children may be used, and the absence of anticholinergic effects (mydriasis, tachycardia, dry skin) supports the diagnosis of poisoning with anticholinesterases.

## Treatment of Acute Toxicity [46, 50, 51]

1. Management of respiratory failure with 100% oxygen and immediate endotracheal intubation.
2. Atropine 2–5 mg (0.05 mg/kg in children) i.v. bolus should be administered every 3–5 min (double the dose if no improvement is seen) until bronchial secretions and wheezing stop. Tachycardia and mydriasis are not contraindications to atropine administration.
3. 2-PAM (pralidoxime) should be administered slowly over 30 min. The World Health Organization recommends a slow bolus of at least 30 mg/kg (approximate).



**Table 5.9** Features of organophosphate (OP) poisoning compound toxicity

Acute toxicity	Intermediate toxicity	Delayed toxicity
<ul style="list-style-type: none"> <li>• Symptoms due to ACh excess—miosis, diarrhoea, bradycardia, bronchospasm, increased bronchial secretions, salivation, sweating and urination (occasionally mydriasis and tachycardia)</li> <li>• Fasciculations, weakness and paralysis</li> <li>• Respiratory failure and cardiovascular collapse</li> </ul>	<ul style="list-style-type: none"> <li>• Occurs approximately 24–96 h after exposure</li> <li>• Mostly seen with lipophilic OP and inadequate dosage of oximes</li> <li>• Neck flexor and extensor weakness, cranial neuropathies, proximal muscle weakness, decreased tendon reflexes, respiratory failure</li> </ul>	<ul style="list-style-type: none"> <li>• Seen 1–3 weeks after specific OPs such as chlorpyrifos, malathion, leptophos, merphos, mipafox, trichlorfon and triethocresyl phosphate</li> <li>• Delayed neuropathy—painful neuropathy followed by symmetrical motor neuropathy</li> </ul>

*Adapted from Sidell [47] and Senanayake and Karalliedde [48]*

mately 2 g) in adults and 25–50 mg/kg in children with continuous infusion at 8 mg/kg/h in adults (10–20 mg/kg/h in children).

4. Diazepam 0.1–0.2 mg/kg i.v. can be used for seizures (repeat as necessary). Prophylactic use of diazepam has been shown to decrease neurocognitive dysfunction after OP poisoning.
5. Aggressive decontamination with complete removal of the patient's clothes and irrigation of the exposed areas should be performed in cases of topical exposure.

## Periodic Paralysis (PP)

Intermittent flaccid muscle weakness with interictal recovery of strength is the characteristic of this heterogeneous group of muscle diseases, collectively termed as periodic paralysis.

### Incidence/Prevalence

Hypokalaemic periodic paralysis has a prevalence of 1 case per 100,000 population in the USA. The prevalence of this entity and other disorders in this category is not known internationally.

Thyrotoxic PP is most common in Asians, with an incidence of 2%, which increases to up to 10% in hyperthyroid patients. Male predominance is notable (85%). PP can be classified as primary or secondary.

General characteristics of primary PP are as follows:

1. It is a hereditary condition.
2. Serum potassium levels are often abnormal.
3. Myotonia may coexist.

**Table 5.10** Primary periodic paralyses

Hypokalaemic PP (hypo PP)	Hyperkalaemic PP (hyper PP)
Calcium-channel mutation (most common—CACNA1S)	Sodium-channel mutation <sup>b</sup> (most common—SCN4A)
Sodium-channel mutation (SCN4A)	Potassium-channel mutation (KCNE3—described in a single family)
Potassium-channel mutation (KCNE3—described in a single family)	Andersen–Tawil syndrome <sup>a</sup> (KCNJ2)
Distal renal tubular acidosis (solute carrier 4—SLC4A mutation)	
Thyrotoxic periodic paralysis (potassium-channel mutation—KCNJ18)	
Andersen–Tawil syndrome <sup>a</sup> (KCNJ2)	

<sup>a</sup>Anderson–Tawil syndrome results from a potassium-channel mutation (70%) and may be associated with hypo, hyper or normokalaemia

<sup>b</sup>Paramyotonia congenita is allelic to hyperkalaemic PP, also caused by a sodium-channel mutation. This disorder is characterized by paradoxical myotonia (myotonia worsening with repetitive exercise) along with mild episodic weakness

**Table 5.11** Secondary periodic paralyses

Hypokalaemic PP (hypo PP)	Hyperkalaemic PP (hyper PP)
Renal potassium-wasting syndrome	Addison disease
– Hyperaldosteronism, Conn syndrome	Chronic renal failure
– Bartter syndrome, liquorice intoxication	Hyporeninemic
Alcohol and drugs—amphotericin B, barium	hypoaldosteronism
Renal tubular acidosis	Ileostomy with a tight stoma
GI potassium-wasting syndrome—laxative abuse and severe diarrhoea	Potassium load
	Potassium-sparing diuretics

A clinically useful classification of PP is shown in Tables 5.10 and 5.11.

## Clinical Features

All PPs are characterized by episodic limb weakness with normal strength interictally. In some forms, patients may develop fixed weakness later in the course of the disorder. Majority of the patients with primary PP become symptomatic before the third decade.

The most common form of primary periodic paralysis is hypokalaemic periodic paralysis and the focus of detailed discussion in this chapter would be limited to this specific entity.

## Hypokalaemic Periodic Paralysis

The clinical features of this entity are given in Box 5.1.

### Box 5.1 Clinical features of hypokalaemic periodic paralysis

1. The onset of episodes is typically in the first or second decade.
2. A history of strenuous exercise or a carbohydrate rich diet on the preceding day followed by severe limb weakness, usually on waking up in the morning, is often provided by the patient.

3. These episodes may also be provoked by stress, infections, fever, menstruation, lack of sleep, fatigue, alcohol, change in barometric pressure or humidity and certain medications (e.g. beta-agonists, insulin and corticosteroids).
4. Patients may experience a prodrome with paraesthesias, fatigue and behavioural changes.
5. Occasionally, the time interval between premonitory symptoms and a full-blown attack is only a few minutes.
6. Patients usually have severe limb weakness, at times accompanied by truncal weakness, on waking up in the morning.
7. The duration can vary from a few hours to almost 1 week, but seldom exceeds 72 h.
8. The attacks are typically intermittent and infrequent in the beginning but can become more frequent where they begin to occur daily.
9. The frequency reduces in the fourth decade rarely occurring after age 50 years. Permanent muscle weakness may be seen later (>40 years of age) and may become severe over a period of time.
10. The occurrence and progression of fixed weakness is independent of the episodic weakness.

## Examination

Weakness is flaccid, the extent of which may vary with the severity of the attack. Sensory deficits are absent. The deep tendon reflexes are diminished during the attacks. Non-fluctuating muscle weakness can occur later even when the attacks have abated. Hypertrophy of the calves has also been observed in some patients.

The clinical features of the other forms of PP are presented in Table 5.12.

## Investigations

### Laboratory Studies

*Hypokalaemic Periodic Paralysis* Serum potassium levels tend to be drop during attacks but may not fall below normal. CPK levels may increase during attacks. A random urine potassium: creatinine ratio (K/C) of <1.5 can be seen in either primary hypokalaemic periodic paralysis (mechanism being shifting of potassium into the cells) or in secondary hypokalaemic periodic paralysis (due to poor intake or gastrointestinal loss). A value of >2.5 can also be seen with secondary hypokalaemic periodic paralysis with urinary potassium wasting being the underlying mechanism. TSH should be checked for a hyperthyroid state.

*Hyperkalaemic Periodic Paralysis* Serum potassium levels are usually elevated and may range from 5–6 mEq/L to upper limit of normal. It seldom reaches cardiotoxic levels. The ECG may show tall T-waves. Low-sodium levels may accompany ele-

**Table 5.12** Clinical features of different types of periodic paralysis (PP)

Syndrome	Age of onset	Duration of attack	Precipitating factors	Severity of attack	Associated features
Hypokalaemic PP	Childhood to third decade	Hours to a week, usually <72 h	As described in the text	Severe, complete paralysis	Fixed muscle weakness seen late in disease
Thyrotoxic–hypo PP	Third and fourth decades	Few hours to 7 days	Same as hypo PP and hyperinsulinemia	Same as hypo PP	May develop fixed muscle weakness
Andersen–Tawil syndrome (hypo or hyper PP)	First and second decades	1 h to days	K <sup>+</sup> intake, exercise, may occur without precipitating factors	Proximal > distal	Cardiac arrhythmias, craniofacial and skeletal anomalies
Hyperkalaemic PP	First decade of life	Few minutes to <2 h (mostly <1 h)	Fasting, cold, alcohol, rest after exercise, trauma, infection, emotional stress, menstrual period	Rarely severe	Paraesthesias, myotonia, occasional pseudohypertrophy of muscles

vated potassium levels. At the end of an attack, lab results may show hypokalaemia, creatinuria and elevated CPK.

### Nerve Conduction Studies

Sensory studies are always normal. Ictally, the motor response amplitude (CMAP) declines, with recovery in the interictal period, worse in hypokalaemic PP.

Hyperkalaemic PP shows a CMAP amplitude decrement on repetitive nerve stimulation (accentuated by cooling) that is steadily progressive without a tendency to recover in contrast with the RNS finding in MG [52].

### Exercise Testing in PP [53]

Short and long exercise tests have been described. An abnormal result is highly suggestive of PP (98% specificity), but does not distinguish different types of PP (hyperkalaemic, hypokalaemic and thyrotoxic PP).

### Needle Electromyography (EMG)

The presence of myotonia is indicative of hyperkalaemic PP and excludes hypokalaemic PP; however, the absence of myotonia does not exclude non-myotonic hyperkalaemic PP. Yield of demonstrating myotonia may be increased by potassium administration and cooling the limb by immersing it in cold water if suspicion for hyperkalaemic PP is high. During a paralytic attack, EMG findings are not specific. Spontaneous activity may be increased with fibrillation potentials and positive sharp waves. In a severe attack, insertional activity disappears as the muscle membrane becomes unexcitable. With voluntary muscle activation, myopathic abnormalities may be seen.

Patients in whom fixed weakness has already developed, myopathic motor units may be noted.

## Therapy

### Medical Care

Acute attacks of hypokalaemic PP often require treatment due to the prolonged duration of the episode and associated severe weakness. In contrast, hyperkalaemic PP are short lived and the weakness is not severe, thus not always requiring acute treatment. Prophylactic treatment in hypokalaemic PP should be considered if the attacks are frequent.

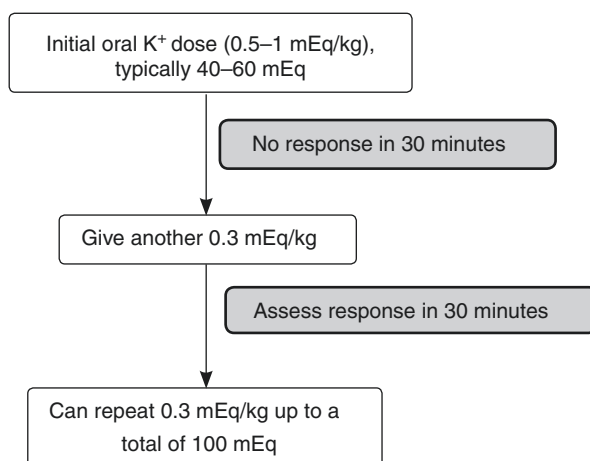
### Hypokalaemic Periodic Paralysis

#### Acute Attack

Severe attacks require treatment as well as monitoring of potassium levels as well as cardiac status. The mainstay of treatment is potassium supplementation. Oral potassium supplementation is preferred over i.v. supplementation which is reserved for patients who are unable to tolerate oral intake. The preferred formulation is potassium chloride in patients with normal renal status [54].

The initial supplementation dose of 0.5–1 mEq/kg of potassium is universally accepted. Quicker correction is achieved by using the aqueous potassium. Some improvement is expected within 30 min of administration. An additional dose of 0.3 mEq/kg may be used in case of poor/no response. This can be repeated up to a total of 100 mEq of potassium (Fig. 5.3). Monitoring of serum potassium is warranted prior to further supplementation. A total dose of 200 mEq in 24 h should not be exceeded since this may result in overcorrection with subsequent hyperkalaemia once the intracellular potassium shifts into the intravascular compartment at the end of the attack.

**Fig. 5.3** Flow chart showing oral potassium supplementation in hypokalaemic periodic paralysis. Serum potassium level should be monitored carefully



Intravenous potassium supplementation is reserved in patients with cardiac arrhythmia or airway compromise. A bolus of potassium chloride in 5% mannitol (0.05–0.1 mEq/kg body weight, up to 10 mEq at one time) may be administered. Infusion of potassium in sodium or dextrose solution has been shown to worsen the attack. Intervals of 20–60 min between infusions should be maintained to avoid overcorrection and resultant hyperkalaemia. Continuous ECG monitoring and repeated serum potassium measurements are mandatory during intravenous supplementation.

### Prophylactic Treatment

#### Carbonic anhydrase inhibitors

Acetazolamide can be used at a dose of 125–1500 mg/day in divided doses [55].

Dichlorphenamide (50–150 mg/day) has been approved in the USA for treatment of periodic paralysis. This can be used as a first line of therapy or in patients who become refractory after initial improvement with acetazolamide.

Patients being treated with carbonic anhydrase inhibitors may need daily supplemental potassium along with.

Potassium-sparing diuretics: triamterene (25–100 mg/day) and spironolactone (25–100 mg/day). These are second-line agents for use in patients with worsening weakness or poor response to carbonic anhydrase inhibitors. Potassium supplements may not be necessary with the use of potassium-sparing diuretics.

Although individual attacks of hypokalaemic PP are lessened by potassium treatment, recurrence is not prevented by prophylactic potassium administration [55].

### Thyrotoxic Periodic Paralysis

Definitive treatment of the underlying cause of thyrotoxicosis is of paramount importance in eradicating this entity. However, in the acute setting, thyrotoxic manifestations can be controlled with the use of non-selective  $\beta$ -adrenergic blockers and intravenous or oral potassium can be used to correct associated hypokalaemia. Furthermore, potassium supplementation and oral  $\beta$ -adrenergic blockers like propranolol can also prevent recurrent episodes. Propranolol in doses of 20–80 mg twice or thrice a day can be used for prophylaxis.

### Hyperkalaemic Periodic Paralysis

This typically does not warrant treatment as the attacks are short lived and usually mild. Carbohydrate rich foods can alleviate the weakness quickly. Beta 2-adrenergic agonists, such as inhaled salbutamol, can also improve the weakness; however, these are contraindicated in the presence of cardiac arrhythmia.

In severe attacks with significant hyperkalaemia or ECG changes, appropriate medical management of hyperkalaemia with bicarbonate, calcium, insulin with dextrose may be needed. Continuous ECG monitoring is always needed during the treatment.

Dichlorphenamide at dose of 50–100 mg twice a day has been approved in the USA as a prophylactic treatment. Other thiazide diuretics and carbonic anhydrase

inhibitors can also be used for prophylaxis. These have been shown to stabilize fluctuations in serum potassium to various stimuli [56]. They are tried as first-line treatment due to their relatively fewer side-effects. Occasionally, they may result in paradoxical hypokalaemic weakness, which responds to potassium supplementation.

### **Andersen–Tawil Syndrome**

Potassium supplementation, potassium-sparing diuretics, beta-adrenergic blockers and carbonic anhydrase inhibitors have all been found to be effective. Implantation of a cardiac defibrillator is rarely needed.

### **Surgical Care**

Hypokalaemic PP patients with calcium channel mutation are susceptible to developing malignant hyperthermia. All patients should be monitored for this potential complication and this should be reported to the anaesthesiologist prior to any surgical planning.

### **Diet**

#### **Hypokalaemic Periodic Paralysis**

Avoidance of high carbohydrate foods and ingestion of low-carbohydrate and low-sodium foods may decrease the frequency of attacks.

#### **Hyperkalaemic Periodic Paralysis**

Ingestion of high carbohydrate diet and sugar candies may improve the weakness during an acute attack.

### **Prognosis**

#### **Hypokalaemic Periodic Paralysis**

The frequency of attacks usually lessens with age. Over a period of time, with recurrent episodes, patients may develop fixed proximal weakness.

#### **Hyperkalaemic Periodic Paralysis**

Some patients may require treatment for myotonia. Life expectancy is not known to be affected.

### **Acute Rhabdomyolysis/Myoglobinuria**

Rhabdomyolysis refers to necrosis of the muscle fibres and release of cellular components into the blood and urine as a result of injury to the sarcolemma. Myoglobinuria refers to an excessive amount of myoglobin in the urine, resulting in cola- or tea-coloured urine, in association with severe muscle damage.

**Table 5.13** Causes of myoglobinuria/rhabdomyolysis

Acquired	Genetic
Altered metabolic states—acidosis, non-ketotic hyperosmolar state, water intoxication	Glycogenolytic/glycolytic disorders—glycogenosis types V, VII, VIII, IX, X, XI
Drugs prescribed: statins, colchicine, neuroleptic drugs resulting in neuroleptic malignant syndrome	Glucose-6-phosphatase dehydrogenase deficiency
Drugs of abuse	Lipid metabolic disorder—deficiencies of carnitine palmitoyltransferase II, short-, medium-, long-chain acyl-CoA dehydrogenase, trifunctional enzyme, medium-chain 3-ketoacyl-CoA and thiolase
Endocrine disorders: hypothyroidism	Mitochondrial myopathies—respiratory chain enzyme deficiencies: succinate dehydrogenase, cytochrome c oxidase, coenzyme Q-10 or lipoamide dehydrogenase
Electrolyte imbalance—hypokalaemia, hypophosphatemia	Muscular dystrophies: dystrophinopathies, $\beta$ -sarcoglycanopathy
Extremes of temperature	Unknown
Infections causing myositis—mostly viral and bacterial, falciparum malaria	
Inflammatory muscle disease—necrotizing autoimmune myopathy, uncommonly—polymyositis, dermatomyositis	
Toxins—snake venom, mushroom poisoning, carbon monoxide poisoning	
Trauma related to—crush injuries, intense exercise, electrical injury, ischemic muscle injury—compartment syndrome	
Uncontrolled/repeated seizures	
Unknown	

*Modified from Sieb JP, Penn AS. Myoglobinuria. In: Engel AG, Franzini-Armstrong C (eds). Myology. McGraw-Hill; 2004: 1663–92*

## Causes

The causes of this entity are outlined in Table 5.13. It is more likely to be hereditary in aetiology if the patient has rhabdomyolysis with minimal exertion or with fasting, a history of multiple episodes or a family history of similar episodes.

## Clinical Features

Clinically, patients experience myalgias followed by diffuse weakness. Patients may report dark-coloured (cola or tea) urine. Examination shows weakness of the extremity muscles with intact sensation. Deep tendon reflexes are preserved. Complications include compartment syndrome and renal failure.

## Investigations

### Laboratory Studies

CPK, liver function, serum electrolytes and renal function need to be monitored. Hypothyroidism should be excluded. CPK may be elevated in levels of up to several



hundreds to thousands. Patients may develop elevated liver enzymes and hyperkalaemia (secondary to muscle breakdown and renal failure). Calcium levels may be reduced or elevated (hypocalcaemia resulting from binding of calcium by damaged muscle, and hyperphosphataemia and hypocalcaemia from release of calcium from the muscle, as well as reduced renal excretion). Hyperphosphataemia results from release of organic and inorganic phosphates from the muscle.

Myoglobin can be detected in the urine and it precedes the rise in the serum CPK. Visible pigmenturia occurs with a level of  $>1$  g/L.

### **Electrodiagnostic Studies**

A nerve conduction study of the sensory and motor nerves is typically normal. EMG findings during rhabdomyolysis are often normal and when abnormal, the changes are subtle. Myopathic motor units may be seen in the proximal muscles in some of the patients.

### **Muscle Biopsy**

This is done for diagnosing a primary muscle disorder. It should be delayed for at least 1 month after the patient has recovered from the acute event.

### **Therapy**

The mainstay of treatment is aggressive hydration to prevent renal failure. The clinical benefits of bicarbonate and mannitol are not clearly established because of conflicting results from various studies [57–64].

Ringer lactate is the preferred fluid of choice as it may reduce the need to use bicarbonate for correcting metabolic acidosis [57]. Renal status needs to be considered when deciding fluid administration goals.

### **Prognosis**

Surprisingly, irreversible injury to the muscle from an episode of myoglobinuria is minimal. Patients with underlying primary muscle disease may have progressive weakness requiring evaluation and appropriate treatment. The prognosis is dependent upon the underlying aetiology and any existing co-morbidities and is best if a precipitating cause can be identified and eliminated.

---

## **Conclusion**

Neuromuscular disorders are often encountered in the emergency department, typically with weakness as the presenting complaint. A detailed history, along with localization of the deficits on physical examination, helps to narrow the differential diagnosis. Accurate diagnosis of the underlying disorder enables institution of appropriate treatment. Evaluation of the patient should be done serially to make prompt diagnosis, manage cardio-respiratory complications and institute appropriate treatment.

## References

1. Hartung HP, Pollard J, Harvey G, et al. Immunopathogenesis and treatment of the Guillain-Barré syndrome. Part 2. Muscle Nerve. 1995;18:154-64.
2. van der Meche FGA, Schmitz PIM. The Dutch Guillain-Barré study group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med*. 1992;326:1123-9.
3. Winer JB, Hughes RAC, Anderson MJ, et al. A prospective study of acute idiopathic neuropathy. Antecedent events. *J Neurol Neurosurg Psychiatry*. 1988;51:613-8.
4. Steininger C, Seiser A, Gueler N, et al. Primary cytomegalovirus infection in patients with Guillain-Barré syndrome. *J Neuroimmunol*. 2007;183:214-9.
5. Orlikowski D, Quijano-Roy S, Sivadon-Tardy V, et al. Campylobacter jejuni and cytomegalovirus (CMV) infections in patients with the Guillain-Barré syndrome. *Arch Pediatr*. 2006;13:1561-5.
6. Visser LH, van der Meche FG, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barré syndrome: the clinical, electrophysiologic, and prognostic features. *Neurology*. 1996;47:668-73.
7. Johnson NT, Crawford SW, Sargur M. Acute acquired demyelinating polyneuropathy with respiratory failure following high dose systemic cytosine arabinoside and marrow transplantation. *Bone Marrow Transplant*. 1987;2:203-7.
8. Eliashiv S, Brenner T, Abramsky O, et al. Acute inflammatory demyelinating polyneuropathy following bone marrow transplantation. *Bone Marrow Transplant*. 1991;8:315-7.
9. Drachman DA, Paterson PY, Berlin BS, et al. Immunosuppression and the Guillain-Barré syndrome. *Arch Neurol*. 1970;23:385-93.
10. Feasby TE. Inflammatory demyelinating polyneuropathies. *Neurol Clin*. 1992;10:651-70.
11. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. *Ann Neurol*. 2010;67:781-7.
12. Sharshar T, Chevret S, Bourdain F, et al. Early predictors of mechanical ventilation in Guillain-Barré syndrome. *Crit Care Med*. 2003;31:278-83.
13. Barohn R, Kissel JT, Warmolts JR, et al. Chronic inflammatory polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. *Arch Neurol*. 1989;46:878-84.
14. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol*. 1990;27:S21.
15. Grand'Maison F, Feasby TE, Hahn AF, et al. Recurrent Guillain-Barré syndrome: clinical and laboratory features. *Brain*. 1992;115:1093.
16. Albers JW, Kelly JJ. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. *Muscle Nerve*. 1989;12:435.
17. Zweig MH, Adornato B, Van Steirteghem AC, et al. Serum creatine kinase BB and MM concentrations determined by radioimmunoassay in neuromuscular disorders. *Ann Neurol*. 1980;7:324-8.
18. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet*. 1997;349:225-30.
19. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. *Ann Neurol*. 1997;41:298-306.
20. Guillain-Barré Syndrome Steroid Trial Group. Double-blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. *Lancet*. 1993;341:586-90.
21. Hughes RA, Swan AV, Raphael JC, et al. Immunotherapy for Guillain-Barré syndrome: a systematic review. *Brain*. 2007;130:2245-57.
22. Lawn ND, Fletcher DD, Henderson RD, et al. Anticipating mechanical ventilation in Guillain-Barré syndrome. *Arch Neurol*. 2001;58:893-8.

23. Wolinsky JS, Cornblath D. The North American study of plasmapheresis in the Guillain-Barré syndrome: The Guillain-Barré syndrome Study Group. *J Clin Apher.* 1985;2:315–20.
24. McKhann GM, Griffin JW, Cornblath DR, et al. Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. *Ann Neurol.* 1988;23:347–53.
25. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology.* 1997;48:1253–60.
26. Grover KM, Sripathi N, Schultz L, et al. Correlation of autoantibodies in myasthenia gravis with phenotypic presentation and disease severity. *Ann Neurol.* 2008;64(Suppl 12):S6.
27. Berroushot J, Baumann I, Kalishewski P, et al. Therapy of myasthenic crisis. *Crit Care Med.* 1997;25:1228–35.
28. Bershad EM, Feen ES, Suarez JI. Myasthenia gravis crisis. *South Med J.* 2008;101:63–9.
29. Mac Duff A, Grant AS. Critical care management of neuromuscular disease, including long term ventilation. *Curr Opin Crit Care.* 2003;9:106–12.
30. Suzuki S, Utsugisawa K, Nagane Y, et al. Classification of myasthenia gravis based on autoantibody status. *Arch Neurol.* 2007;64:1121–4.
31. Seybold ME. Treatment of myasthenia gravis. In: Engel AG, editor. *Myasthenia gravis and myasthenic disorders*, vol. 8. Oxford: Oxford University Press; 1999. p. 167–201.
32. Bedlack RS, Sanders DB. How to handle myasthenic crisis: essential steps in patient care. *Postgrad Med J.* 2000;107:211–2.
33. Hickling KG, Walsh J, Henderson S, et al. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med.* 1994;22:1568–78.
34. Gadjos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Ann Neurol.* 1997;41:789–96.
35. Qureshi AI, Choudhry MA, Akbar MS, et al. Plasma exchange versus intravenous immunoglobulin treatment for myasthenic crisis. *Neurology.* 1999;52:629.
36. Jani-Acsadi A, Lisak RP. Myasthenic crisis: guideline for prevention and treatment. *J Neurol Sci.* 2007;261:127–33.
37. Pascuzzi RM, Coslette HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol.* 1984;15:291–8.
38. Ahmed S, Kirmani JF, Janjua N, et al. An update on myasthenic crisis. *Curr Treat Options Neurol.* 2005;7:129–41.
39. Panda S, Goyal V, Behari M, et al. Myasthenic crisis: a retrospective study. *Neurol India.* 2004;52:453–6.
40. Seneviratne J, Mandrekar J, Wijedicks EF, et al. Predictors of extubation failure in myasthenic crisis. *Arch Neurol.* 2008;65:929–33.
41. Agarwal R, Aggarwal AN, Gupta D, et al. Low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenomation. *Emerg Med J.* 2005;22:397–9.
42. Sanmuganathan PS. Myasthenic syndrome of snake envenomation: a clinical and neurophysiological study. *Postgrad Med J.* 1998;74:596–9.
43. Bomb BS, Roy S, Kumawat DC, et al. Do we need anti snake venom (ASV) for management of elapid ohitoxaemia? *J Assoc Physicians India.* 1996;44:31–3.
44. Harsoor SS, Gurudatta CL, Balabhaskar S, et al. Ventilatory management of patients with neuroparalytic envenomation. *Indian J Anaesth.* 2006;50:452–5.
45. Eddleston M, Phillips MR. Self poisoning with pesticides. *BMJ.* 2004;328:42.
46. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev.* 2003;22:165.
47. Sidell FR. Soman and sarin: clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7:1.
48. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med.* 1987;316:761.
49. Arrieta DE, Mccurdy SA, Henderson JD, et al. Normal range of human red cell acetylcholinesterase activity. *Drug Chem Toxicol.* 2009;32:182–5.

50. Eddleston M, Roberts D, Buckley N. Management of severe organophosphorus pesticide poisoning. *Crit Care*. 2002;6:259.
51. Tuovinen K. Organophosphate-induced convulsions and prevention of neuropathological damages. *Toxicology*. 2004;196:31.
52. Streib EW. AAEE minimonograph #27: differential diagnosis of myotonic syndromes. *Muscle Nerve*. 1987;10:603–15.
53. Fournier E, Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol*. 2004;56:650–6.
54. Levitt JO. Practical aspects in the management of hypokalemic periodic paralysis. *J Transl Med*. 2008;6:18.
55. Griggs RC, Engel WK, Resnick JS. Acetazolamide treatment of hypokalemic periodic paralysis. Prevention of attacks and improvement of persistent weakness. *Ann Intern Med*. 1970;73:39–48.
56. Hoskins B, Vroom FQ, Jarrell MA. Hyperkalemic periodic paralysis. Effects of potassium, exercise, glucose and acetazolamide on blood chemistry. *Arch Neurol*. 1975;32:519–23.
57. Cho YS, Lim H, Kim SH. Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. *Emerg Med J*. 2007;24:276–80.
58. Ron D, Taitelman U, Michaelson M, et al. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med*. 1984;144:277–80.
59. Better OS, Rubinstein I, Winaver JM, et al. Mannitol therapy revisited (1940–1997). *Kidney Int*. 1997;52:886–94.
60. Visweswaran P, Massin EK, Dubose TD Jr. Mannitol-induced acute renal failure. *J Am Soc Nephrol*. 1997;8:1028–33.
61. Kellum JA. The use of diuretics and dopamine in acute renal failure: a systematic review of the evidence. *Crit Care*. 1997;1:53–9.
62. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet*. 2005;365:417–30.
63. Vanholder R, Sever MS, Ereke E, et al. Rhabdomyolysis. *J Am Soc Nephrol*. 2000;11:1553–61.
64. Holt SG, Moore KP. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. *Intensive Care Med*. 2001;27:803–11.

# Movement Disorders in the Emergency

# 6

Madhuri Behari and Vibhor Pardasani

---

## Introduction

Movement disorders classically have an insidious onset and slow progression and are usually not associated with emergency situations. Infrequently, there do arise rapidly evolving movement disorders or acute complications of existing movement disorders that need immediate attention and rapid management which can be life-saving [1, 2]. This chapter deals with the clinical presentation, diagnosis and management of some common movement disorders presenting to the emergency department (ED).

---

## Classification

Although there is no formal classification of movement disorder emergencies, we shall use the following broad subtypes for a practical approach:

1. Acute presentations/exacerbations of specific movement disorders (Table 22.1)
  - (a) Acute parkinsonism
  - (b) Dystonic storm/status dystonicus
  - (c) Oculogyric crisis
  - (d) Malignant catatonia
  - (e) Hemiballism-hemichorea
  - (f) Tic emergencies
  - (g) Abductor paresis in multiple system atrophy.

---

M. Behari (✉)

Consultant Neurologist, Fortis Hospital, Vasant Kunj, New Delhi, India

V. Pardasani

Department of Neurology, Seven Hills Hospital, Mumbai, Maharashtra, India

**Table 22.1** Acute presentations/exacerbations of specific movement disorders

Condition	Treatment
1. Acute parkinsonism	Levodopa/dopamine agonists/anticholinergics
(a) Infectious	Manage infectious conditions with antimicrobials
(b) Toxic	Discontinue exposure to culprit drug/toxin
2. Dystonic storm	(a) Benzhexol, tetrabenazine, pimozide, baclofen, chlorpromazine, sodium valproate, carbamazepine
	(b) Sedate with propofol/midazolam
	(c) Institute paralysis and ventilation if not responding
	(d) If still refractory, consider surgical options
3. Oculogyric crisis	Intravenous diphenhydramine/other anticholinergics/clonazepam
4. Malignant catatonia	(a) Fluid replacement, temperature reduction and support of cardiac, respiratory and renal functions
	(b) Withhold antipsychotics
	(c) Benzodiazepines
	(d) Electroconvulsive therapy
	(e) ACTH/corticosteroids
	(f) Dantrolene
5. Hemiballism-hemichorea	(a) Treatment of the underlying cause
	(b) Tetrabenazine/haloperidol
	(c) Clonazepam, valproic acid, trihexyphenidyl, amitriptyline
6. Tic emergencies	(a) Discontinue culprit drug, if any
	(b) Pimozide/haloperidol
	(c) Botulinum toxin-A (BTX-A) for refractory vocal tics
7. Abductor paresis in MSA	(a) CPAP
	(b) BTX-A, surgical options
	(c) Emergency tracheostomy or a tracheal intubation

## 2. Drug-induced emergencies

- (a) Neuroleptic malignant syndrome
- (b) Parkinsonism-hyperpyrexia syndrome
- (c) Serotonin syndrome
- (d) Acute dystonia
- (e) Acute drug-induced akathisia.

## Acute Presentation of Specific Movement Disorders (Table 22.1)

### Acute Parkinsonism

Parkinsonism is usually a chronic condition, and patients present to the outpatient clinics and very rarely to the ED. However, acute parkinsonism can be encountered as a syndrome secondary to an identifiable, non-degenerative disorder. Most secondary forms of parkinsonism, including the drug-induced forms, usually evolve over weeks, but may sometimes develop over hours to days. Acute presentation is

typically seen after the administration of agents that deplete/block dopamine, after viral encephalitis, or after carbon monoxide or cyanide poisoning [3, 4].

## Infectious Parkinsonism

Parkinsonism may occur following infection with viruses that target the substantia nigra. Von Economo was the first to recognize and classify three distinct forms of the acute illness, which he called ‘encephalitis lethargica’, now also called von Economo disease (ED): the somnolent-ophthalmoplegic form, the hyperkinetic form and the amyostatic-akinetic form [5]. No causative agent was ever identified for this encephalitis. Parkinsonism may occasionally accompany Japanese B encephalitis, HIV encephalopathy, encephalitis caused by Coxsackie B virus, rubella, influenza virus, cytomegalovirus, measles, St Louis encephalitis, Western equine encephalitis, West Nile virus, Epstein–Barr virus, mycoplasma pneumonia, syphilis, borreliosis (Lyme disease), basal ganglia abscesses or granulomas caused by toxoplasmosis, cryptococcosis, mucormycosis, cysticercosis and tuberculosis [4, 6, 7]. In addition to supportive measures during the acute encephalopathic phase, the timely administration of an appropriate antibiotic/antiviral agent, in proper dosage and for an appropriate duration of time, is of paramount importance in parkinsonism associated with known viral or bacterial encephalitis. When the symptoms persist, one may have to use levodopa, either alone or in combination with other adjunctive anti-parkinsonism agents, such as anticholinergics and dopamine agonists. Patients admitted as cases of encephalitis frequently receive antipsychotics and anti-epileptics for the control of behaviour and seizures, respectively. In such a setting, it is important to recognize and discontinue the culprit drugs causing parkinsonism before one can consider the possibility of an infectious/post-infectious aetiology, and initiate anticholinergic or dopaminergic agents.

## Acute Toxic Parkinsonism

An acute parkinsonian state can be produced by many toxins, including MPTP, organophosphate pesticides, carbon monoxide, carbon disulphide, cyanide and methanol [4, 8]. The last four are similar, in that parkinsonism is accompanied by severe encephalopathy. There are no tremors and the condition is poorly responsive to levodopa. Acute parkinsonism has been reported to occur following bone marrow transplantation, and treatment with high-dose cytosine arabinoside, cyclophosphamide, total body irradiation, amphotericin B, paclitaxel, vincristine and adriamycin [4]. Flunarizine, a commonly used migraine prophylactic agent, is also associated with a syndrome of acute parkinsonism, especially in the elderly.

Management consists of preventing further exposure to the culprit toxin and the institution of specific antidotes, wherever possible. Symptomatic treatment in the form of levodopa, dopamine agonists and anticholinergics may be required for a variable period of time.

### Points to Remember

- Parkinsonism can sometimes present acutely as a complication of encephalitis or exposure to toxins.
- Management should focus on the treatment of causative factors, viz. antimicrobials in the case of infectious parkinsonism and removal of the incriminating toxin in the case of toxic parkinsonism.
- Levodopa, dopamine agonists and anticholinergic agents can be offered as symptomatic treatment in such cases.

## Dystonic Storm/Status Dystonicus

### Introduction and Clinical Features

Dystonias are characterized by patterned involuntary sustained or intermittent muscle contractions causing repetitive twisting movements, abnormal postures or both. When severe muscle contractions become increasingly frequent or continuous, a patient is said to be in status dystonicus or dystonic storm [1, 2]. In practice, status dystonicus often occurs at the end of a continuum of worsening dystonia. At times, status dystonicus may present as a new onset dystonic disorder without previous history of similar movements. Status dystonicus is known to affect all age groups but up to 60% of patients are between ages 5 years and 16 years, with a male preponderance [9].

The spasms are extremely painful, at times interfering with respiration and causing metabolic disturbances, such as hyperpyrexia, dehydration, respiratory insufficiency and acute renal failure secondary to rhabdomyolysis. The contractions can be either sustained with abnormal postures, hence called tonic or rapid and repetitive dystonic, hence phasic. The tonic dystonic storms have worse outcomes. Respiratory failure can result from one or a combination of dystonic bulbar spasms (pharyngeal, laryngeal), truncal-respiratory muscle spasms, diaphragm dystonia, generalized exhaustion, aspiration pneumonia, and indeed the need for highly sedative and relaxant drugs used to control status dystonicus.

### Causes and Pathophysiology

Acquired dystonias are likely to present with status dystonicus (38% of cases), CP being the most common individual secondary cause followed by the 'heredodegenerative dystonias' (particularly neurodegeneration with brain iron accumulation, Wilson disease, and mitochondrial disorders) and the 'pure primary dystonias' [10]. The precipitating factors include trauma, surgery, infection, fever, anaesthesia, 'metabolic disorder' decompensation, stress, pain, gastro-oesophageal reflux disease, constipation, puberty-related deterioration in CP and abrupt introduction, withdrawal or change in medical treatment. The trigger might not be identified in around 30% cases.

Certain drugs are known to trigger status dystonicus especially the dopamine-receptor blockers pimozide and haloperidol. Both these agents are frequently used to treat dystonia and chorea. Metoclopramide can have the same effect [11]. In



Wilson disease the introduction of chelation therapy with penicillamine, zinc sulphate, or trientine has also been implicated in status dystonicus [12, 13]. Introduction of clozapine, as well as withdrawal of lithium and tetrabenazine, is also known to be associated with status dystonicus [9]. Severe dystonia can sometimes be precipitated by deep brain stimulation failure caused by hardware problems, intrathecal baclofen pump failure as well as routine baclofen, and benzodiazepine withdrawal in general should be considered where relevant [13–15].

## Investigations

The investigations are targeted at elucidating the precipitating factor as well as the primary cause of dystonia, if it is not already known. They include routine haematology and biochemistry; wet blood film for acanthocytes; assessment of uric acid, copper and ceruloplasmin, serum lactate and pyruvate, plasma and urinary amino acids; syphilis serology and CSF examination, including lactate [9, 16].

## Management

It is necessary to institute paralysis, ventilation and sedation in most cases of status dystonicus to avert bulbar and respiratory complications, and to relieve the severe exhaustion and excruciating pain that results from the incessant dystonic spasms. After a period of 4–6 days, the infusion of the paralyzing and sedating agents can be tailed off to assess the underlying dystonic spasms. Intravenous fluid resuscitation, antibiotics, nutritional requirements (nasogastric or parenteral) and antipyretics need to be provided in most patients. Rhabdomyolysis, if already set in, requires specific therapy in the form of intravenous fluids, urine alkalinization, dantrolene, neuromuscular paralysis and/or dialysis in acute renal failure [17].

Status dystonicus becomes life-threatening as sustained active muscle contraction leads to exhaustion and rhabdomyolysis. One of the goals of management is to achieve muscle relaxation without compromising respiration. For mild cases, clonidine in adults (1–5 µg/kg up to 3 hourly) and chloral hydrate in children (30–100 mg/kg, administered 3–6 hourly) are used for this purpose. For moderate and severe case, deeper sedation and stronger muscle relaxation are frequently required to achieve prompt resolution of the dystonic spasms. A benzodiazepine, i.e. continuous intravenous midazolam (0.02–0.1 mg/kg/h) is the preferred agent with the advantages of rapid onset of action, short half-life and easy titratability. For refractory spasms, anaesthetic agents like propofol (0.5–3.0 mg/kg/h) are used along with non-depolarizing muscle paralyzing agents. Depolarizing agents, e.g. suxamethonium being associated with rhabdomyolysis are to be avoided [16–18].

While the patient is intubated, periodic evaluation of the patient's true clinical state and response to anti-dystonia measures should be done by tapering off the infusions. As paralytic ileus is a potential serious complication of both status dystonicus and the multiple drugs used in its management, it is important to minimize the combination of drugs used, the doses, though high, but titrated against oxygen saturations, heart rate and blood pressure [16, 17].

Specific anti-dystonia drugs: The preferred agents are an anticholinergic (trihexyphenidyl), a dopamine blocker (haloperidol or pimozide) and a catecholamine

depleter (tetrabenazine). Gabapentin has been found to be of remarkable benefit in refractory status dystonicus associated with Wilson disease and can be tried in that associated with other aetiologies [13].

Other agents used in anecdotal way with limited success include benzodiazepines like clonazepam, flurazepam, diazepam, oral baclofen, levodopa, or levodopa-carbidopa, sodium valproate, carbamazepine, primidone, phenytoin, acetazolamide, benztropine, biperiden, lithium, bromocriptine, chlorpromazine, olanzapine, clozapine and risperidone [9, 17].

The response to oral anti-dystonia drugs is generally reported to be poor, with significant risk to patients who develop dependence on sedative or anaesthetic agents and remain in refractory status dystonicus. Therefore, more invasive surgical therapies including intrathecal baclofen (ITB), deep brain stimulation (DBS) or pallidotomy are now considered early, once acute systemic infections have been either excluded or treated. Intrathecal baclofen (ITB) therapy has been successfully used in refractory cases of SD [15, 17]. Tolerance may potentially limit the use of ITB over long periods. ITB, although less invasive than brain surgery, is also known to be associated with risks such as over-dosage, withdrawal syndrome and catheter migration/ breakage. Deep brain stimulation of the bilateral globes pallidus internal has been found to be an effective treatment for SD in the majority of treated patients [14, 19]. Benefit has been reported to occur usually within days or weeks. It has largely replaced the lesions procedures of pallidotomy, thalamotomy and pallido-thalamotomy for the treatment of dystonia. However, if DBS is not available, unilateral pallidotomy could be considered [19, 20].

### Points to Remember

- Dystonic storm or status dystonicus consists of severe and potentially fatal exacerbations of dystonic conditions.
- These are usually triggered by trauma, surgery, infection, fever, abrupt introduction/withdrawal or change in medical treatment.
- In most cases, it is necessary to institute paralysis with assisted ventilation and sedation to avoid bulbar and respiratory complications while instituting anti-dystonia therapy.
- DBS, unilateral pallidotomy or ITB should be considered early in refractory SD.

## Oculogyric Crisis

### Introduction

An oculogyric crisis is characterized by tonic conjugate ocular deviation that may last from a few minutes to many hours. Oculogyric crisis can occur both in acute and tardive dystonia [1].

### Causes and Pathophysiology

Oculogyric crisis (OGC) is most commonly seen following exposure to neuroleptics. Tetrabenazine, gabapentin, domperidone, carbamazepine and lithium carbonate

have all been reported to trigger OGC [1, 2, 21]. There are reports of OGC associated with structural brain lesions, such as bilateral paramedian thalamic infarction, herpes encephalitis, cystic glioma of the posterior third ventricle and as the initial manifestation of Wilson disease [21].

## Management

Regardless of its cause, OGC can be terminated with an injection of intravenous diphenhydramine (25–50 mg). Oral clonazepam may be effective for patients with chronic neuroleptic-induced OGC that is resistant to anticholinergics [21].

## Malignant Catatonia

### Introduction and Clinical Features

Catatonia may be conceptualized as a continuum, with milder forms at one end (termed simple or benign) and more severe forms, with hyperthermia and autonomic dysfunction (termed malignant catatonia or MC), at the other [22]. Stuporous catatonia is characterized by varying combinations of mutism, immobility and waxy flexibility; the associated features include posturing, negativism, automatic obedience, ‘echo’ phenomena—echolalia and echopraxia, hyperthermia, altered consciousness, autonomic instability manifested by diaphoresis, tachycardia, labile or elevated blood pressure and varying degrees of cyanosis [22, 23]. Catatonics remain alert in stark contrast to the somnolence or decreased level of consciousness seen in all other forms of stupor.

### Causes and Pathophysiology

Organic causes of catatonia include cerebrovascular disorders involving the anterior cingulate gyri or temporal lobes, normal-pressure hydrocephalus, cerebral anoxia, subacute sclerosing panencephalitis in stage I, glioma involving the splenium of the corpus callosum, closed head trauma, surgical removal of lesions near the hypothalamus, viral encephalitis, bacterial meningo-encephalitis, septicaemia, hyperthyroidism, Addison disease, Cushing disease, Wernicke encephalopathy and sedative-hypnotic withdrawal [22, 23].

### Investigations

Investigations are targeted to exclude medical or drug-induced causes of MC with the help of clinical features and neuroimaging. The most consistent laboratory findings in MC include elevation of the creatine kinase level and leucocytosis. Elevation in serum transaminases, generalized slowing on electroencephalogram, hyperglycaemia, elevated serum creatinine, hyponatraemia, hypernatraemia and dehydration are not uncommon [22, 24].

## Management

Management involves early institution of intensive medical care focusing on fluid replacement, temperature reduction, and support of cardiac, respiratory and renal

functions [22, 23]. Antipsychotics should be withheld. Catatonia is best managed with benzodiazepines. If simple catatonia proves unresponsive to benzodiazepines after 1–2 days of treatment, electroconvulsive therapy (ECT) should be considered. Electroconvulsive therapy appears effective, however, only if initiated before severe progression of the symptoms. ACTH or corticosteroids may be tried if ECT proves ineffective. Dantrolene, a drug that inhibits contraction and heat production in muscle, may also be administered. It should be started at a minimum dose of 1 mg/kg, the maximum cumulative dose being 10 mg/kg. The oral dosage is 4–8 mg/kg/day, in three or four divided doses. In MC occurring as a consequence of a medical illness, treatment must be directed at the underlying disorder [2, 22, 23].

### Points to Remember

- Catatonia is characterized by mutism, immobility, waxy flexibility, posturing, negativism and ‘echo’ phenomena.
- Causes are diverse and must be excluded by a detailed history, neuroimaging, CSF studies and other investigations.
- Management consists of fluid replacement, temperature reduction, and support of cardiac, respiratory and renal functions, along with the administration of benzodiazepines.
- Refractory cases may require ECT.

## Hemiballism-Hemichorea

### Introduction

Hemiballism refers to large-amplitude, flinging, at times violent movements of one side of the body [25]. As acute hemiballismus resolves over days to weeks, the movements often become choreiform. Stroke is the single most common cause of hemiballism with localization being classically in the contralateral subthalamic nucleus or rarely deep white matter. Hemiballism associated with non-ketotic hyperglycaemia is the second most common cause. With this disorder, chorea or ballism may be unilateral or bilateral. It occurs more in women, and it may sometimes be the initial presentation of diabetes mellitus. Other conditions reported to have caused acute onset hemiballism-hemichorea include neoplastic metastases and primary CNS tumours; infections, especially with cryptococcal granuloma, toxoplasmosis and tuberculoma; SLE—often with anticardiolipin antibodies; scleroderma; Behçet disease; Sydenham chorea; medications, including oral contraceptives, levodopa and ibuprofen; vascular: including cavernous angioma and post-surgical complications [1, 3, 25].

### Clinical Features

Hemiballistic movements increase with action and stress and are only rarely suppressible for more than a few seconds and disappear in sleep [25]. In patients with hyperglycaemic chorea, as the blood glucose is corrected, the disorder usually resolves completely, although mild symptoms persist for more than 3 months in 20% of

patients [25, 26]. Hemichorea refers to movements that are lower in amplitude than hemiballismus, affecting both the distal and proximal limbs; are classically irregular jerky quasi-purposive.

## Management

Treatment of the underlying cause may resolve the hemiballismus, although severely affected patients may still require concomitant pharmacological therapy. If stroke is the cause, standard stroke management, such as antiplatelet therapy, and secondary preventive measures, such as control of blood pressure and normalization of blood sugar, must be implemented. Padding of the affected limb and the management of systemic complications, such as exhaustion, dehydration and rhabdomyolysis, are mainstays of treatment. In the very rare case of extremely severe hemiballismus causing dangerous complications, patients may require sedation or even intubation with neuromuscular blockade as a temporary bridge until effective pharmacological therapy is instituted. Tetrabenazine is the preferred symptomatic treatment for patients with persistent hemiballismus. The dosage can start at 12.5 mg two or three times daily and be titrated upward to a maximum of 250 mg per day. If tetrabenazine is unavailable, ineffective or associated with severe side-effects, or if the patient has a history of severe depression, typical neuroleptics should be tried. Haloperidol is the favoured drug and is started at a dosage of 0.5–1 mg twice daily, to be titrated upwards as needed. In emergency situations, it can be given as an intramuscular dose of 1 mg. If this is ineffective, 2 mg can be repeated 4 h later. There have been reports of effective treatment with clonazepam, valproic acid, trihexyphenidyl and amitriptyline. If effective, treatment should be maintained for a period of approximately 3 months, after which the medication should be gradually withdrawn [25, 26].

## Points to Remember

- Hemiballismus consists of flinging movements of unilateral proximal limb.
- Stroke and non-ketotic hyperglycaemia are common causes.
- Hyperglycaemic hemiballismus-hemichorea resolves with correction of blood glucose.

## Tic Emergencies

Tics are sudden, brief, intermittent repetitive and stereotypic movements (motor tics) or sounds (vocal or phonetics) usually affecting children [1, 27]. They are temporarily suppressible, often preceded by a premonitory sensation or an urge to perform them, and usually produce a sense of relief. As the long-term history of tics is generally benign, the primary aim of treatment is to maintain a child in the school environment so as to achieve near-normal socialization. Rarely, tics are severe enough to cause a neurological emergency. At times, intensely frightening exacerbations may occur in the context of the waxing and waning course of a tic disorder. The drugs reported to exacerbate tics include methylphenidate, pemoline, levodopa,

phenytoin, carbamazepine, lamotrigine, phenobarbital, imipramine, clomipramine, fluoxetine, sertraline, amphetamine and cocaine; discontinuation of the precipitating agent reverses the problem [1, 27]. If there is no such causative agent, drugs for tic suppression may be warranted. As pimozide is more effective and better tolerated than haloperidol, it is the treatment of choice for acute, disabling tics. The lowest possible dose, 1 mg in the case of pimozide and 0.25 mg in the case of haloperidol, should be used. Disruptive vocal tics can be managed with intralaryngeal botulinum toxin injections [28, 29]. Tic disorders can cause various types of acute pain syndromes, including pain resulting from the actual performance of the tic (such as neck pain caused by sudden neck movements); pain resulting from a traumatic injury due to being struck by a body part involved in tics; pain caused by the effort of tic suppression (excessive isometric muscle contraction); self-inflicted pain in order to reduce tic expression and pain caused by behavioural abnormalities accompanying the tic disorder, such as self-mutilating compulsions.

The chronic tic patient may present for an urgent consultation because of the onset of new abnormal movements secondary to anti-tic medications. As opposed to tics that are generally perceived as 'voluntary' and suppressible, patients usually perceive tardive dystonic or choreic movements as 'involuntary' and not suppressible. Unlike tics, dystonic or choreic movements remain unchanged or even increase during distraction or the performance of skilled tasks. Usually, a significant decrease in the neuroleptic medication is required to achieve relief of movements like akathisia. If the neuroleptic dose cannot be reduced, the addition of anticholinergics, amantadine or  $\beta$ -blockers may be helpful. At times, patients may present to the emergency room with loud, uncontrollable barking, yelping, shouting of obscenities or other vocal utterances. Parenteral neuroleptics may be required to control such severe phonic tics. Botulinum toxin A (BTX-A) injections into the thyroarytenoids have been shown to be a particularly useful option for patients with severe, loud and disabling involuntary vocalizations [29, 30].

### Points to Remember

- Tics are sudden, brief, intermittent, repetitive and temporarily suppressible stereotypic movements.
- When exacerbated by drugs, acute tics are managed by discontinuation of the precipitating agent.
- Tics can also be managed with pimozide and haloperidol.
- One needs to differentiate tics from drug-induced dyskinesias and akathisia.

## Abductor Paresis in Multiple System Atrophy

### Introduction and Clinical Features

The onset of stridor, initially at night but later throughout the day, is a grave symptom in the setting of atypical parkinsonism, especially multiple system atrophy (MSA). The mean survival is less than 1 year. Classic abductor paresis (AP) can appear at any time in the course of MSA, even as an initial or an isolated symptom.

## Causes and Pathophysiology

Neurogenic atrophy of the posterior cricoarytenoid muscle, which is the abductor of the vocal cords, is caused by neuronal loss in the nucleus ambiguus. In patients with MSA and AP, inspiratory negative pressure caused by diaphragmatic contraction occurs concurrent with or even before a full opening of the vocal glottis, because of the delay in abduction. Paradoxical movement of the vocal cords occurs with inspiratory adduction and expiratory abduction [31, 32].

## Investigations and Management

Diagnosis of MSA is made on the basis of clinical criteria. A definite diagnosis of AP is made by fibre optic laryngoscopy, performed both during wakefulness and sleep. If the larynx is the culprit and the spasm is severe, an emergency tracheostomy is indicated. Nasal continuous positive air pressure at night can successfully treat nocturnal stridor and apnoea in patients who choose not to undergo tracheostomy. Other therapeutic options include arytenoidectomy, cord lateralization, cordectomy and BTX-A injection into the adductors [1].

## Course and Prognosis

Abductor paresis usually takes two different courses: slowly progressive and rapidly progressive. In the former, there is a gradual deterioration over 1–3 years as a result of paralytic denervation of the abductor. In the rapidly progressive type, an emergency tracheostomy or a tracheal intubation is often needed, even if the patient is already known to have AP [1].

## Points to Remember

- Stridor due to abductor paresis is a common complication of MSA.
- It is caused by neurogenic atrophy of the posterior cricoarytenoid muscle.
- Emergency tracheostomy may be required for acute management.

---

## Drug-Induced Emergencies (Table 22.2)

### Neuroleptic Malignant Syndrome

#### Introduction and Clinical Features

Neuroleptic malignant syndrome (NMS) is a drug-induced disorder resulting from exposure to neuroleptics that act by blocking dopamine receptors. Both typical and atypical neuroleptics are known to be associated with NMS. Other medications such as prochlorperazine, metoclopramide, amoxapine, tetrabenazine, droperidol, lithium and promethazine are also implicated. Although the incidence of NMS is 0.02–3.2% among patients prescribed antipsychotic medications, it is important to recognize this potentially fatal reaction (mortality rate 5–20%). It is characterized by rigidity, fever, autonomic instability and altered level of consciousness [31–34]. The other signs include catatonia, tachycardia, tachypnoea, labile blood pressure, dysarthria, dysphagia, diaphoresis, sialorrhoea, incontinence, myoclonus, tremors

**Table 22.2** Drug-induced emergencies

Condition	Treatment
1. Neuroleptic malignant syndrome	(a) Discontinue the antipsychotic (b) Parenteral hydration (c) External cooling (d) Bromocriptine, dantrolene or amantadine (e) ECT for refractory cases
2. Parkinsonism-hyperpyrexia syndrome	(a) Re-institute the discontinued drug (b) Intravenous levodopa/apomorphine
3. Serotonin syndrome	(a) Discontinuation of the precipitating drugs (b) Benzodiazepines (c) Cyproheptadine
4. Acute dystonia	Anticholinergic drugs
5. Acute drug-induced akathisia	Beta-blockers, anticholinergics, benzodiazepines, clonidine, vitamin B <sub>6</sub>

and elevation of serum creatine kinase. Symptoms often begin after initiation or an increase in the antipsychotic dose. NMS increases in severity over 48–72 h and lasts 2–14 days. The differential diagnoses include CNS infections, porphyria and tetanus.

Medical complications of NMS include renal failure from rhabdomyolysis, respiratory failure from decreased chest wall compliance, potentially fatal arrhythmias, aspiration pneumonia and other complications of immobility such as deep venous thrombosis, pulmonary embolism and pressure sores.

### Causes and Pathophysiology

Neuroleptic-induced dopamine blockade in different parts of the brain accounts for the various features of NMS. Dopamine reduction in the hypothalamus causes fever and autonomic instability; in the nigrostriatal system it leads to rigidity; and reduction in corticolimbic dopamine activity accounts for the altered consciousness [34–36]. However, the dopaminergic blocking theory alone does not explain why NMS develops at a given time in a given patient. There are probably other genetic, constitutional, environmental and pharmacological factors that interact to produce the syndrome [36].

### Treatment

The most critical step in the treatment is to recognize the clinical features of the syndrome and discontinue the antipsychotic drug without delay. Supportive interventions include cooling blankets for fever, cardiac monitoring, monitoring for urine output and renal function, and parenteral rehydration [37]. Haemodialysis may be required in the case of acute renal failure associated with myoglobinuria. Trials of bromocriptine, dantrolene or amantadine may be helpful for patients with moderate to severe symptoms [38]. Bromocriptine in a dosage of 5–10 mg thrice a day provides relief from the symptoms, especially muscle rigidity. Other *dopaminergic agents* including carbidopa/levodopa, ropinirole and pramipexole are likely effective.



Muscle relaxant dantrolene, classically used in malignant hyperthermia, is helpful in decreasing rigidity, hyperthermia and tachycardia. The usually recommended dosage is 1–3 mg/kg/day orally or intravenously, in four divided doses. *Anticholinergics* are generally best avoided as they may impair heat dissipation in febrile patients. *Benzodiazepines* may be useful for agitation and rigidity. *Electroconvulsive therapy* can be useful when the NMS symptoms are refractory or when there is a need for psychiatric treatment owing to a prolonged absence of antipsychotic pharmacotherapy [38].

Most patients with NMS respond to the discontinuation of antipsychotics and fluid replenishment. Treatment should continue for 7–10 days depending on the half-life of the culprit antipsychotic. It is recommended to wait for at least 2 weeks before re-starting antipsychotics after NMS has cleared as 1/3rd of the patients may relapse if the antipsychotics are re-started too early.

### Points to Remember

- NMS is a life-threatening complication of the use of neuroleptics, both typical and atypical.
- It is characterized by fever, rigidity, confusion, autonomic instability and raised creatine kinase.
- Most patients respond to discontinuation of the neuroleptic agent, along with supportive measures.

## Parkinsonism-Hyperpyrexia Syndrome

### Introduction and Clinical Features

Parkinsonism-hyperpyrexia syndrome (PHS) is clinically indistinguishable from NMS except that it occurs in patients with pre-existing parkinsonism, in whom levodopa or other dopaminergic drugs are suddenly withdrawn or altered [39]. Time of onset of the symptoms after change in dopaminergic therapy ranges from 18 h to 7 days. Initial feature in most patients is severe rigidity, along with tremor and dys-autonomia. Within 72–96 h, most patients are febrile and have an altered mental status, ranging from agitation and confusion to stupor and coma [39, 40]. After the inciting event, the period between latency and the onset of symptoms is usually twice as long (93 h vs. 49 h) for PHS as for NMS. NMS is a more aggressive disorder than PHS, and carries a poorer prognosis [40].

### Causes and Pathophysiology

Hypodopaminergic state usually triggers the syndrome, as in NMS. Parkinsonism-hyperpyrexia syndrome has been seen in patients of Parkinson disease following sudden cessation or even partial withdrawal of dopaminergic therapy or when regimens of medication are changed. With the advent of bilateral subthalamic nucleus stimulation for advanced Parkinson disease, similar presentations have occurred when stimulators were accidentally turned off [39]. It can also be precipitated by aggressive medication adjustments after DBS surgery in PD. It is important to recognize that DBS surgery does not protect the patient from PHS.

## Management

As in NMS, any patient presenting with ‘febrile encephalopathy’ and extrapyramidal features must also undergo brain imaging to exclude encephalitis or structural lesions. Creatine kinase and white blood cells are usually not as elevated as in NMS associated with neuroleptic use. When discontinuation of medication is the cause, the drug most commonly responsible is levodopa, and it should be re-instituted, via a nasogastric tube if necessary, at the same dosage as earlier. When nasogastric feeding is contraindicated because of a gastrointestinal problem such as ileus, intravenous levodopa infusion can be started. 50–100 mg of levodopa should be infused using an infusion pump over 3 h, and this should be repeated 3–4 times a day until oral intake of levodopa becomes possible. If an intravenous formulation of levodopa is unavailable, apomorphine injections may be tried at a dosage of 1.0–2.0 mg/h [41]. The rest of the management is similar to that of NMS, including rehydration with intravenous fluids and treatment of hyperthermia with antipyretics and cooling blankets, as well as supportive measures such as mechanical ventilation, cardiovascular monitoring and prevention of thrombophlebitis. Because these patients are at risk for infections such as aspiration pneumonia, it is reasonable to initiate antibiotic therapy while awaiting the work-up. Additional medical therapy with bromocriptine or other dopamine agonists and dantrolene should be utilized at the same dosages as for NMS. Steroid pulse therapy might shorten the course of the illness. Electroconvulsive therapy has also been successfully tried in refractory cases [41].

## Prevention

If reduction in dopaminergic therapy is needed, gradual reduction is mandated and patients should be made aware of the possible occurrence of PHS. This applies to patients with idiopathic Parkinson disease as well as those with Parkinson plus syndrome or secondary parkinsonism receiving levodopa therapy.

## Points to Remember

- PHS resembles NMS and occurs on sudden discontinuation or change of dosage of anti-parkinsonian drugs.
- Fever, altered mental status and rigidity are the characteristic features.
- It responds to re-institution of the previous dosage of levodopa/dopamine agonist drug.
- Recovery is more rapid and complete than in NMS.

## Serotonin Syndrome

### Introduction and Clinical Features

The serotonin syndrome is a largely under-recognized, potentially life-threatening adverse drug reaction that results from overstimulation of serotonin (5-HT) receptors by various serotonergic agents. The clinical features include fever with

tremors, shivering, diaphoresis, myoclonus, hyperreflexia, changes in behaviour, hypertension, mydriasis, hyperactive bowel sounds and horizontal ocular clonus [42, 43].

### Causes and Pathophysiology

Serotonin syndrome is thought to result from stimulation of the 5-HT<sub>1a</sub> and 5-HT<sub>2</sub> receptors [44]. The drugs associated with the serotonin syndrome include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), opiate analgesics, valproate, linezolid, sibutramine, ondansetron, metoclopramide, sumatriptan, methylene dioxymethamphetamine (MDMA, or 'ecstasy') and lysergic acid diethylamide (LSD) [42].

### Management

Management of the serotonin syndrome entails discontinuation of the precipitating drugs, in addition to supportive care. Agitation usually needs to be controlled with benzodiazepines. Cyproheptadine, a 5-HT<sub>2a</sub> antagonist, is a specific therapy, although its efficacy has not been rigorously established [44, 45]. After an initial dose of 12 mg, 2 mg of cyproheptadine is administered every 2 h if the symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every 6 h. In most cases, the serotonin syndrome is a self-limiting condition that improves on cessation of the offending drugs. In severe cases, patients require intensive care as the syndrome may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and/or adult respiratory distress syndrome [44].

### Points to Remember

- Acute onset fever, tremors, myoclonus, hyperreflexia, changes in behaviour, hypertension and hyperthermia in a patient taking 2 or more serotonergic medication(s) should raise the suspicion of serotonin syndrome.
- The treatment consists of discontinuation of the offending drug(s) and the administration of cyproheptadine.

## Acute Neuroleptic-Induced Dystonia

### Introduction and Clinical Features

Dystonia is a movement disorder characterized by sustained muscle contractions producing torsional and repetitive movements or abnormal postures [46]. Acute dystonia can be in the form of orofacial dystonia, back arching, neck extension and even life-threatening laryngospasm. Acute dystonic reactions are most common after injectable high-potency antipsychotics, but also occur shortly after the introduction of oral antipsychotics and occasionally, after an increase of dosage [47]. Dystonia begins within 24 h of exposure, and 90% of reactions occur within 5 days. Acute dystonia is more likely to occur with typical antipsychotics (6%)

than the newer atypical drugs (1–2%) [48]. A form of acute dystonic reaction characterized by tonic lateroflexion of the trunk, appearing 3–10 days after starting dopamine-blocking agents, is known as the Pisa syndrome [47].

### **Pathophysiology**

Dopaminergic blockade results in relative cholinergic overactivity, leading to dystonia. There may also be paradoxical dopaminergic hyperfunction induced through blockade of presynaptic dopamine receptors [48, 49].

### **Management**

Acute dystonic reactions may be prevented by the use of anticholinergic drugs. Patients at high risk for acute dystonia (young patients, cocaine abusers, AIDS patients, those with a previous/family history of dystonia) requiring antipsychotics may be prescribed prophylactic anticholinergics [50]. Acute dystonia responds well to injectable anticholinergic drugs, notably diphenhydramine (25 or 50 mg). The response to this is so consistent that if a patient with suspected drug-induced acute dystonia fails to respond, an alternative diagnosis should be considered [49].

### **Points to Remember**

- Neuroleptic use may be complicated by acute dystonic reactions in susceptible individuals.
- These may be managed with anticholinergics and prevented by prophylactic anticholinergics.

## **Acute Drug-Induced Akathisia**

### **Introduction and Clinical Features**

Akathisia literally means ‘inability to remain seated’. Drug-induced acute akathisia is defined as a subjective feeling of restlessness and an intensely unpleasant need to move, occurring secondary to antipsychotic treatment. Akathisia is estimated to occur in 20–75% of patients treated with conventional antipsychotics [50, 51]. Atypical antipsychotics are less likely to cause akathisia. It tends to occur within the first 4 weeks of initiating or increasing the dosage of antipsychotic medication. Patients with akathisia tend to have subjective complaints of ‘inner restlessness’, most often in the legs. This is manifested as fidgeting, frequent changes in posture, crossing and uncrossing of the legs, rocking while sitting, marching in place and shuffling when walking. Akathisia is often associated with dysphoria, anxiety and irritability. Akathisia in a psychotic patient can easily be mistaken for worsening of psychotic features, which may cause the clinician to increase the dosage of the antipsychotic, exacerbating the akathisia [49].

## Management

The initial approach is to try and reduce the risk of developing akathisia by minimizing the dosage of antipsychotic medication. The use of atypical antipsychotics should be considered because they are associated with a lower risk of akathisia. Specific anti-akathic drugs can be initiated. These include beta-blockers, anticholinergics, benzodiazepines, clonidine and vitamin B<sub>6</sub> [52].

## Points to Remember

- Acute akathisia is a not so uncommon complication of neuroleptic use.
- Reducing the dosage of conventional antipsychotics and preferential use of atypical antipsychotics can prevent most such reactions.

## Conclusion

Although most movement disorders have a chronic presentation, physicians need to be familiar with the recognition and management of acute movement disorders in the emergency. These may sometimes be life-threatening. A detailed history, including a history of the drugs used by the patient, is vital for the recognition of individual conditions. Although treatment is usually supportive, early recognition and management of the precipitating factors, along with well-tailored symptomatic management, are vital in determining the prognosis.

Table 22.3 gives details of drugs used in the treatment of various movement disorders.

**Table 22.3** Drugs used in the treatment of various movement disorders

Drug	Dosage	Adverse events	Interactions
Carbidopa/ levodopa	TID: 25 mg carbidopa + 100 mg levodopa ('25/100' tablet), half a tablet twice or three times a day MD: 200–1200 mg levodopa • No dosage adjustment is required for patients with renal or hepatic insufficiency • Avoid in pregnancy	<ul style="list-style-type: none"> <li>• Cardiac arrhythmias</li> <li>• Orthostatic hypotension</li> <li>• Nausea, vomiting</li> <li>• Peripheral oedema</li> <li>• Psychosis, confusion</li> </ul>	<ul style="list-style-type: none"> <li>• Neuroleptic drugs reduce the effect of levodopa</li> <li>• Levodopa enhances the effect of any drugs that lower blood pressure</li> <li>• Risk of cardiac arrhythmias with volatile liquid anaesthetics, such as halothane</li> </ul>

(continued)

**Table 22.3** (continued)

Drug	Dosage	Adverse events	Interactions
Bromocriptine	TID: 1.25 mg twice a day MD: 3.75–40 mg Avoid in pregnancy	<ul style="list-style-type: none"> <li>• Confusion, euphoria, agitation, anxiety</li> <li>• Nausea, vomiting</li> <li>• Cardiac arrhythmias, hypotension</li> <li>• Polyuria, incontinence</li> <li>• All the ergotamine derivatives can cause pulmonary, retroperitoneal and pericardial fibrosis</li> </ul>	Dopamine agonists must be avoided in patients with psychiatric disease or dementia. The elderly are at particular risk for confusion Metoclopramide antagonizes the effects of these drugs Dopa agonists enhance the effect of any drugs that lower blood pressure Risk of cardiac arrhythmias with volatile liquid anaesthetics, such as halothane
Ropinirole	TID: 0.25 mg three times a day MD: 1.5–24 mg Avoid ropinirole in patients with severe renal insufficiency Reduce the dose of ropinirole in severe hepatic insufficiency	<ul style="list-style-type: none"> <li>• Confusion, euphoria, agitation, anxiety</li> <li>• Nausea, vomiting</li> <li>• Cardiac arrhythmias, hypotension</li> <li>• Polyuria, incontinence</li> <li>• Obsessive behaviour, pathological gambling</li> </ul>	
Amantadine	TID: 100 mg per day MD: 200–400 mg per day Reduce the dose of amantadine in patients with moderate renal insufficiency		<ul style="list-style-type: none"> <li>• Dopamine antagonists may diminish the effectiveness</li> </ul>
Apomorphine	Should be used as subcutaneous injections only, not for i.v. use as i.v. crystallization leads to thrombus formation and pulmonary embolism TID: 0.2 ml (2 mg) Maximum dose: 0.6 ml (6 mg) Starting dose should be reduced to 1 mg when administering to patients with mild or moderate renal impairment	<ul style="list-style-type: none"> <li>• Nausea, vomiting</li> <li>• Orthostatic hypotension, syncope</li> <li>• Prolongs the QT/QTc interval, causes torsades de pointes</li> <li>• Hallucinations, somnolence</li> <li>• May cause dyskinesia or exacerbate pre-existing dyskinesia</li> <li>• Priapism</li> <li>• Injection site reactions including bruising, granuloma and pruritus</li> </ul>	<ul style="list-style-type: none"> <li>• Concomitant use of apomorphine with drugs of the 5HT<sub>3</sub> antagonist class such as ondansetron is contraindicated as it causes profound hypotension and loss of consciousness</li> <li>• Caution should be exercised when prescribing apomorphine concomitantly with drugs that prolong the QT/QTc interval</li> </ul>

**Table 22.3** (continued)

Drug	Dosage	Adverse events	Interactions
<i>Anticholinergics</i>			
Trihexyphenidyl HCl	TID: 1 mg twice a day MD: 2–15 mg Although not contraindicated for patients with cardiac, liver or kidney disorders, or with hypertension, such patients should be maintained under close observation It should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy	<ul style="list-style-type: none"> <li>• Dryness of the mouth, blurring of vision, dizziness, nausea, vomiting</li> <li>• Mental confusion, agitation, disturbed behaviour</li> <li>• Constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilatation of the pupil, increased intraocular tension, weakness, vomiting and headache</li> </ul>	
Diphenhydramine	10–50 mg i.v. at a rate not exceeding 25 mg/min or deep i.m. Maximum daily dose: 400 mg Antihistamine therapy is contraindicated in nursing mothers		
<i>Dopamine depleter</i> Tetrabenazine	TID: 25 mg per day MD: 50–200 mg per day <ul style="list-style-type: none"> <li>• Dosage should be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers</li> <li>• Contraindicated in hepatic impairment</li> <li>• Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus</li> </ul>	<ul style="list-style-type: none"> <li>• Sedation/somnolence/fatigue</li> <li>• Orthostatic hypotension</li> <li>• Hyperprolactinaemia</li> <li>• Akathisia</li> <li>• Increase in the corrected QT interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia</li> <li>• Depression, suicidal tendencies</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated in patients taking monoamine oxidase inhibitors</li> <li>• Should be avoided in combination with other drugs that are known to prolong QTc</li> <li>• Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetrabenazine should be halved</li> </ul>

(continued)

**Table 22.3** (continued)

Drug	Dosage	Adverse events	Interactions
<i>Sedative-hypnotics</i> Propofol	Initial IV bolus of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg i.v. (25% of initial dosage) as needed to achieve the desired level of sedation Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available	<ul style="list-style-type: none"> <li>• Respiratory depression</li> <li>• Hypoxaemia</li> <li>• Hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• May produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics</li> </ul>
<i>Benzodiazepines</i>			
Midazolam	0.01–0.05 mg/kg for induction of sedation For maintenance of sedation, the usual initial infusion rate is 0.02–0.1 mg/kg/h	<ul style="list-style-type: none"> <li>• Respiratory depression</li> <li>• Hypoxaemia</li> <li>• Hypotension</li> </ul>	May produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole; these may result in prolonged sedation due to a decrease in plasma clearance of midazolam



**Table 22.3** (continued)

Drug	Dosage	Adverse events	Interactions
Clonazepam	TID: 0.25–0.5 mg per day Maximum dose: 20 mg per day		
<i>Skeletal muscle relaxant</i> Dantrolene	Oral: 4–8 mg/kg per day Intravenous: TID: 1 mg/kg MD: 10 mg/kg per day • Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	<ul style="list-style-type: none"> <li>• Decrease in grip strength and weakness of leg muscles</li> <li>• Lightheadedness</li> <li>• Liver dysfunction</li> <li>• Thrombophlebitis</li> <li>• Pulmonary oedema</li> </ul>	<ul style="list-style-type: none"> <li>• If patients judged malignant hyperthermia susceptible are administered dantrolene, avoidance of known triggering agents must be done</li> <li>• Combination with calcium-channel blockers can precipitate cardiac arrhythmias</li> </ul>
<i>Antipsychotics</i>			
Haloperidol	Oral TID: 0.25 mg per day MD: 5–20 mg per day Parenteral: 2–5 mg	<ul style="list-style-type: none"> <li>• Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness</li> <li>• Tachycardia, hypotension and hypertension</li> <li>• Extrapyramidal symptoms including dystonia, tardive dyskinesia</li> <li>• Neuroleptic malignant syndrome (NMS)</li> <li>• Tachycardia, hypotension and hypertension</li> <li>• QT-prolongation and torsades de pointes</li> </ul>	<p>Haloperidol should be administered cautiously to patients:</p> <ul style="list-style-type: none"> <li>• with severe cardiovascular disorders</li> <li>• receiving anticonvulsant medications because haloperidol may lower the convulsive threshold</li> </ul>

(continued)

**Table 22.3** (continued)

Drug	Dosage	Adverse events	Interactions
Pimozide	TID: 1 mg per day MD: 5–10 mg per day		
<i>Serotonin blocker</i> Cyproheptadine	TID: 0.25 mg/kg per day MD: 4–32 mg per day Contraindicated in nursing mothers	<ul style="list-style-type: none"> <li>• Sedation and sleepiness</li> <li>• Disturbed coordination</li> <li>• Acute labyrinthitis, blurred vision, diplopia,</li> <li>• Hypotension, palpitation, tachycardia</li> <li>• Dryness of nose and throat,</li> <li>• Urinary frequency, difficulty in urination, urinary retention</li> </ul>	<ul style="list-style-type: none"> <li>• MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines</li> <li>• Should be used with caution in patients with history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease and hypertension</li> </ul>

*TID* treatment initiating dose, *MD* maintenance dose, *MAO* monoamine oxidase

## References

1. Poston KL, Frucht SJ. Movement disorder emergencies. *J Neurol*. 2008;255(Suppl 4):2–13.
2. Frucht SJ. Movement disorder emergencies. *Curr Neurol Neurosci Rep*. 2005;5:284–93.
3. Kipps CM, Fung VS, Grattan-Smith P, et al. Movement disorder emergencies. *Mov Disord*. 2005;20:322–34.
4. Fernandez HH, Friedman JH. Acute parkinsonism. In: Frucht SJ, Fahn S, editors. *Movement disorder emergencies: diagnosis and treatment*. Totowa: Humana Press; 2005. p. 9–28.
5. Howard RS, Lees AJ. Encephalitis lethargica: a report of four recent cases. *Brain*. 1987;110:19–33.
6. Mirsattari SM, Power C, Nath A. Parkinsonism with HIV infection. *Mov Disord*. 1998;13:684–9.
7. Pradhan S, Pandey N, Shashank S, et al. Parkinsonism due to predominant involvement of substantianigra in Japanese encephalitis. *Neurology*. 1999;53:1781–6.
8. Choi IS. Parkinsonism after carbon monoxide poisoning. *Eur Neurol*. 2002;48:30–3.
9. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. *Brain*. 1998;121:243–52.
10. Fasano A, Ricciardi L, Bentivoglio AR, et al. Status dystonicus: predictors of outcome and progression patterns of underlying disease. *Mov Disord*. 2012;27:783–8.
11. Mishra D, Singhal S, Juneja M. Status dystonicus a rare complication of dystonia. *Indian Pediatr*. 2010;47:883–5.
12. Svetel M, Sternic N, Pejovic S, Kostic VS. Penicillamine-induced lethal status dystonicus in a patient with Wilson's disease. *Mov Disord*. 2001;16:568–9.
13. Paliwal VK, Gupta PK, Pradhan S. Gabapentin as a rescue drug in D-penicillamine-induced status dystonicus in patients with Wilson disease. *Neurol India*. 2010;58:761–3.
14. Apetauerova D, Schirmer CM, Shils JL, Zani J, Arle JE. Successful bilateral deep brain stimulation of the globus pallidus internus for persistent status dystonicus and generalized chorea. *J Neurosurg*. 2010;113:634–8.

15. Muirhead W, Jalloh I, Vloeberghs M. Status dystonicus resembling the intrathecal baclofen withdrawal syndrome: a case report and review of the literature. *J Med Case Rep.* 2010;4:294.
16. Vaamonde J, Narbona J, Weiser R, et al. Dystonic storms: a practical management problem. *Clin Neuropharmacol.* 1994;17:344–7.
17. Nirenberg MJ, Ford B. Dystonic storm. In: Frucht SJ, editor. *Movement disorder emergencies: diagnosis and treatment.* 2nd ed. New York: Springer/Human Press; 2013. p. 125–35.
18. Mariotti P, Fasano A, Contarino MF, et al. Management of status dystonicus: our experience and review of the literature. *Mov Disord.* 2007;22:963–8.
19. Jech R, Bares M, Urgosik D, et al. Deep brain stimulation in acute management of status dystonicus. *Mov Disord.* 2009;24:2291–2.
20. Zorzi G, Marras C, Nardocci N, et al. Stimulation of the globus pallidus internus for childhood-onset dystonia. *Mov Disord.* 2005;20:1194–200.
21. Sacks OW, Kohl M. L-dopa and oculogyric crises. *Lancet.* 1970;296:215–6.
22. Philbrick KL, Rummans TA. Malignant catatonia. *J Neuropsychiatry Clin Neurosci.* 1994;6:1–13.
23. Fricchione G, Bush G, Fozdar M, et al. Recognition and treatment of the catatonic syndrome. *J Intensive Care Med.* 1997;12:135–47.
24. Fricchione G, Mann SC, Caroff SN. Catatonia, lethal catatonia, and neuroleptic malignant syndrome. *Psychiatr Ann.* 2000;3:347–55.
25. Dewey RB, Jankovic J. Hemiballism–hemichorea. *Arch Neurol.* 1989;46:862–7.
26. Lee B, Hwang S, Chang G. Hemiballismus-hemichorea in older diabetic women: a clinical syndrome with MRI correlation. *Neurology.* 1999;52:646–8.
27. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community based study. *Neurology.* 2002;59:414–20.
28. Jankovic J. Tourette's syndrome. *N Engl J Med.* 2001;345:1184–92.
29. Scott B, Jankovic J, Donovan D. Botulinum toxin into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. *Mov Disord.* 1996;11:431–3.
30. Jankovic J. Botulinum toxin in the treatment of dystonic tics. *Mov Disord.* 1994;9:347–9.
31. Isono S, Shiba K, Yamaguchi M, et al. Pathogenesis of laryngeal narrowing in patients with multiple system atrophy. *J Physiol.* 2001;536:237–49.
32. Hughes RG, Gibbin KP, Lowe J. Vocal fold abductor paralysis as a solitary and fatal manifestation of multiple system atrophy. *J Laryngol Otol.* 1998;112:177–8.
33. Caroff SN, Mann SC. Neuroleptic malignant syndrome. *Med Clin North Am.* 1993;77:185–202.
34. Velamoor VR, Norman RM, Caroff SN, et al. Progression of symptoms in neuroleptic malignant syndrome. *J Nerv Ment Dis.* 1994;182:168–73.
35. Keck PE, Pope HG, Cohen BM, et al. Risk factors for neuroleptic malignant syndrome. *Arch Gen Psychiatry.* 1989;46:914–8.
36. Mann SC, Caroff SN, Fricchione G, et al. Central dopamine hypoactivity and the pathogenesis of the neuroleptic malignant syndrome. *Psychiatr Ann.* 2000;30:363–74.
37. Davis JM, Caroff SN, Mann SC. Treatment of neuroleptic malignant syndrome. *Psychiatr Ann.* 2000;30:325–31.
38. Caroff SN, Mann SC, Keck PE Jr. Specific treatment of the neuroleptic malignant syndrome. *Biol Psychiatry.* 1998;44:378–81.
39. Mizuno Y, Takubo H, Mizuta E, et al. Malignant syndrome in Parkinson's disease: Concept and review of the literature. *Parkinsonism Relat Disord.* 2003;9(Suppl 1):S3–9.
40. Harada T, Mitsuoka K, Kumagai R, et al. Clinical features of malignant syndrome in Parkinson's disease and related neurological disorders. *Parkinsonism Relat Disord.* 2003;9(Suppl 1):S15–23.
41. Ikebe S, Harada T, Hashimoto T, et al. Prevention and treatment of malignant syndrome in Parkinson's disease: a consensus statement of the malignant syndrome research group. *Parkinsonism Relat Disord.* 2003;9(Suppl 1):S47–9.
42. Mackay FJ, Dunn NR, Mann RD. Antidepressants and the serotonin syndrome in general practice. *Br J Gen Pract.* 1999;49:871–4.

43. Dunkley EJ, Isbister GK, Sibbritt D, et al. The hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96:635–42.
44. Isbister GK, Whyte IM. Serotonin toxicity and malignant hyperthermia: role of 5-HT<sub>2</sub> receptors. *Br J Anaesth*. 2002;88:603–4.
45. Radomski JW, Dursun SM, Revely MA, et al. An exploratory approach to the serotonin syndrome; an update of clinical phenomenology and revised diagnostic criteria. *Med Hypotheses*. 2000;55:218–24.
46. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text Revision. Washington DC: American Psychiatric Association; 2000.
47. Ayers JL, Dawson KP. Acute dystonic reactions in childhood to drugs. *N Z Med J*. 1980;92:464–5.
48. Raja M, Azzoni A. Novel antipsychotics and acute dystonic reactions. *Pharmacol Biochem Behav*. 2000;67:497–500.
49. Sachdev PS. Neuroleptic-induced movement disorders: an overview. *Psychiatr Clin North Am*. 2005;28:255–74.
50. Keepers GA, Casey DE. Clinical management of acute neuroleptic-induced extrapyramidal syndromes. In: Masserman JH, editor. *Current psychiatric therapies*. New York: Grune & Stratton; 1986. p. 139–57.
51. Miller CH, Fleischacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Saf*. 2000;22:73–81.
52. Hu S, Frucht S. Emergency treatment of movement disorders. *Curr Treat Options Neurol*. 2007;9:103–14.

# Neurological Emergencies in the Immunocompromised Population

# 7

Ajitesh Ojha and Saša A. Živković

## Introduction

Neurological emergencies are a significant source of morbidity and mortality in immunocompromised patients. Immunodeficiency can be attributed to congenital and acquired causes. Congenital immunodeficiencies can either be combined with involvement of both cellular and humoral immunity or restricted to impairment of either type. Common combined immunodeficiency syndromes include ataxia telangiectasia, Wiskott Aldrich syndrome, and DiGeorge syndrome whereas X linked agammaglobulinemia and common variable immunodeficiency are characterized by isolated impaired humoral immunity. As opposed to rare patients with congenital immunodeficiencies, acquired immunodeficiencies are much more common (Table 7.1). Acquired immunodeficiency is seen in HIV patients, diabetics, and in various patients treated with immunosuppressive, cytotoxic, and antirejection medications (e.g., transplant recipients, patients with autoimmune disorders, and cancer). These people are at increased risk of various neurologic emergencies including opportunistic CNS infections, posterior reversible encephalopathy syndrome (PRES), immune reconstitution inflammatory syndrome (IRIS), epilepsy, and stroke.

## CNS Infections

CNS infections can present in a variety of ways clinically including meningitis, encephalitis, meningoencephalitis, and abscesses. Patients' symptoms range from fever, headache, nuchal rigidity, focal neurological deficits (seizures, paralysis), and cognitive impairment to coma and death. However, due to decreased immune response, early symptoms and signs might be missed in immunocompromised

---

A. Ojha · S. A. Živković (✉)

Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

e-mail: [ojhaa@upmc.edu](mailto:ojhaa@upmc.edu); [zivkovics@upmc.edu](mailto:zivkovics@upmc.edu)

**Table 7.1** Common risk factors and conditions affecting immunocompetence (modified from Linden [1])

<i>Medications</i>
Chemotherapy
Calcineurin inhibitors
Anti TNF $\alpha$ therapy
Steroids
<i>Infectious/congenital/oncologic disorders</i>
HIV
Lymphoma/Leukemia
Hypogammaglobulinemia
Functional asplenia
<i>Autoimmune conditions</i>
Connective tissue disorders
Autoimmune neuromuscular conditions (myasthenia, CIDP)
Other autoimmune conditions (inflammatory bowel disorders, psoriasis)
<i>Metabolic disturbances</i>
Diabetes
Liver failure
Renal failure
Malnutrition
Total parenteral nutrition

patients or the symptoms might be overall milder than expected. In addition to typical pathogens, these patients are also at risk of infection with more diverse opportunistic microorganisms usually not seen in immunocompetent population (Table 7.2) [1]. The risk of infection is determined by the extent of immunosuppression and exposure to various pathogens, and the environmental exposure will differ depending on geographic area and climate [2, 3]. Timely diagnosis and early treatment are essential for effective management and CSF studies and imaging patterns (Fig. 7.1) are helpful in evaluation of immunocompromised patients with new neurologic symptoms and possible opportunistic CNS infections (Table 7.3).

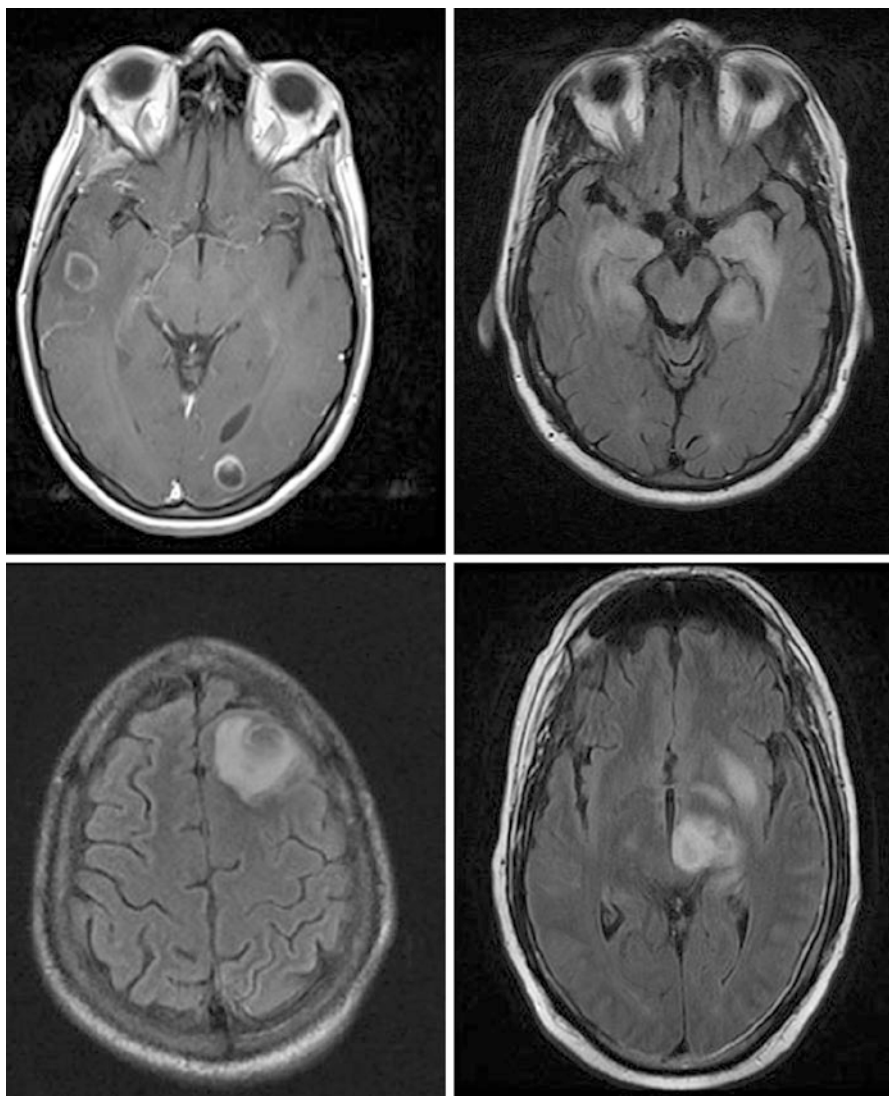
While spectrum of opportunistic CNS infections is similar with various types of immunosuppression, the time window of greater risk of opportunistic CNS infections in transplant recipients differs depending whether patients underwent (hematologic) stem cell or solid organ transplants.

In stem cell transplant recipients, the risk of opportunistic infection is usually highest in the first 3 months after transplantation, which is characterized by the neutropenic-preengraftment phase (2–4 weeks) and the early post-engraftment phase (4 weeks–3 months) before reconstitution of the immune system. This is a result of predominance of cell mediated and humoral deficiencies during this time period. After the first 3 months, chronic graft versus host disease and severe community acquired infections are more common [1]. Subsequent chronic risk of opportunistic infections is greater with allogeneous stem cell transplantation when compared to autologous stem cell recipients as immunosuppression is needed to prevent graft rejection.

**Table 7.2** Opportunistic CNS infections in various immunosuppressed populations (modified from Linden [1])

	Meningitis	Meningoencephalitis	Encephalitis	Mass lesion
Chemotherapy	<i>S. pneumoniae</i> <i>S. aureus</i> <i>E. coli</i> <i>P. aeruginosa</i>	<i>L. monocytogenes</i>	HSV	Aspergillus, Nocardia Cryptococcus Pyogenic bacteria
Bone marrow transplant		<i>L. monocytogenes</i> <i>C. neoformans</i> <i>S. stercoralis</i> HHV-6	HSV CMV VZV JC virus	Aspergillus Nocardia Mycoses Tuberculosis Toxoplasma
Solid organ transplant		<i>L. monocytogenes</i> Cryptococcus HHV6	HSV CMV VZV West Nile virus JC virus	Aspergillus Nocardia Mycobacteria
HIV	<i>S. pneumoniae</i>	Toxoplasma	JC virus	Toxoplasma Mycobacteria Cryptococcus
B lymphocyte defects	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>N. meningitidis</i>			
Natalizumab			JC virus	

In contrast, solid transplant patients are at higher risk of infection after the first month of transplant due to the gradual but cumulative effect of iatrogenic immunosuppression. In the first month, infections are related to pre-transplant colonization, transplant procedure, and allograft transmission. After the acute period (1–6 months), opportunistic CNS infections caused by viral pathogens such as CMV, EBV, HSV, and HHV-6 become more frequent, usually presenting as encephalitis or meningoencephalitis as well as other systemic diseases. During this period, there is also an increased risk of infection with opportunistic non-viral pathogens such as Aspergillus, Nocardia that can lead to the formation of space occupying brain lesions such as abscesses. After more than 6 months since transplantation, community acquired infections and opportunistic CNS infections due to pathogens such as Cryptococcus, Nocardia, Pneumocystis carinii, and Listeria become more prevalent [4]. CNS infections are a major cause of morbidity and mortality with one study finding them to be the strongest independent predictors of mortality in heart transplant patients in the long term [5]. Risk of infections may increase with allograft rejection when higher doses of antirejection medications are used. However, the risk of CNS infections has steadily decreased with the use of improved immunosuppressive regimens, with incidence rates as low as 1% in more recent patient cohorts [6].



**Fig. 7.1** Neuroimaging of CNS infections. (*Top left*): Multiple ring-enhancing lesions on T1-weighted imaging with *Candida albicans* brain abscesses. (*Top right*): Bilateral temporal lobe hyperintensities on T2-FLAIR MRI sequence in patient with HHV-6 encephalitis. (*Bottom left*): Left frontal lobe hyperintensity on T2-weighted imaging with CNS toxoplasmosis. (*Bottom right*): Left thalamic hyperintensity on T2-FLAIR MRI sequence with progressive multifocal encephalopathy

### Viral Infections

AIDS patients, especially those with CD4 counts less than 200, are not only susceptible to infections caused by common viral pathogens (HSV, VZV, EBV, CMV) and fungal microorganisms (*Cryptococcus*), but also to less common viral pathogens such as JC virus as well as parasites including *Toxoplasma*. Common viruses that



**Table 7.3** Clinical features of fungal infections in various patient populations [17]

Etiology of immunosuppression	Fungal agents	Clinical presentation
Solid organ transplants	Candida Aspergillus Cryptococcus	Meningitis, abscess Abscess, infarction Meningoencephalitis
Bone marrow transplant/ corticosteroids	Aspergillus Mucormycosis	Abscess, infarction Sinus involvement, abscess, infarction
HIV, TNF- $\alpha$ inhibitors	Cryptococcus Histoplasma	Meningoencephalitis Meningitis
Neutropenia	Candida Aspergillus	Meningitis, abscess Abscess, infarction
Immunocompetent	Blastomyces Histoplasma Coccidioides	Meningitis, abscess Meningitis, abscess Meningitis, meningoencephalitis

cause infections in the immunosuppressed include HSV, HHV6, EBV, VZV, CMV, and JC virus. The most common clinical presentation for all of them is the development of meningitis and/or encephalitis. *HSV virus* has two common subtypes, HSV1 and HSV2 with the CNS infections caused by former almost universally presenting with encephalitis seen in adults and older children. HSV preferentially affects the mesial temporal lobes showing up as T2 weighted hyperintensities or restricted diffusion on MRI imaging. CSF examination helps establish the diagnosis by exhibiting lymphocytic pleocytosis with increased protein, normal glucose, and a positive CSF HSV PCR. The degree of protein elevation is a marker of disease duration. PCR is the gold standard for diagnosis of viral CNS infections, and CSF PCR has a sensitivity of 98% and specificity of 94% in diagnosing CNS HSV infections [7]. Given the temporal lobe predilection, there is presence of either lateralized temporal periodic discharges or temporal sharp waves on electroencephalography. The consensus treatment for HSV encephalitis is 10 mg/kg IV acyclovir Q8H for 14–21 days. Mortality at 3 months is 15% with age (greater and less than 30) and decreased level of consciousness negative prognostic factors. While HSV1 usually causes encephalitis, HSV2 is more likely to cause meningitis. Some patients may also have recurrent episodes of aseptic meningitis (Mollaret meningitis). Recently, there has also been some evidence linking HSV encephalitis to postinfectious NMDA encephalitis [8].

Similar radiographic findings can also be seen with limbic encephalitis caused by HHV6 but imaging can also be normal in these patients.

*Varicella zoster virus* (VZV) is known to cause several varied neurological presentations in both the central and peripheral nervous system manifesting as meningoencephalitis, cranial nerve palsies, myelopathy, or vasculopathy. The diagnosis of VZV infection is often suspected if patients have the characteristic dermatomal rash. However, it can cause any of its presentations even in the absence of rash. In those cases, CSF evaluation is helpful. CSF usually shows a lymphocytic pleocytosis with normal glucose and elevated protein. Virologic tests that are more specific in diagnosis are VZV IgM/IgG in CSF as well as VZV IgM in serum. Treatment of VZV infections in immunocompromised individuals is based on IV acyclovir, and duration may be extended in individual patient cases (e.g., more severe immunodeficiency) [9].

*CMV infections* are often seen in immunocompromised patients and neurological presentations of opportunistic CNS infections include encephalitis or polyradiculopathy. In transplant patients, *EBV virus* can cause post-transplant lymphoproliferative disorder and less commonly EBV encephalitis, myelitis, radiculitis, and peripheral neuropathy. *West Nile virus* is seen in both immunocompetent and immunocompromised patients but immunocompromised patients are at significantly higher risk of severe complications [10]. Transmission of the virus is usually through mosquito bites but can also rarely occur secondary to an infected allograft. West Nile virus can lead to various clinical presentations including encephalitis, motor neuronopathy, aseptic meningitis, tremor, facial palsy, parkinsonism, and myoclonus. On MRI, common findings include T2 hyperintensities in the white matter, thalamus, and substantia nigra.

*Progressive multifocal leukoencephalopathy (PML)* is a demyelinating disorder due to the JC virus. The JC virus is a polyoma virus that is thought to be possibly transmitted through the fecal-oral route and is found in various cell types including brain cells and epithelial cells of the kidney. While the JC virus is usually not pathogenic, it is thought to transform through an unclear mechanism in infected individuals. There is evidence that the incidence of PML is correlated to the degree of immunosuppression in patients with the disease [11]. Demyelination in PML is a result of destruction of infected oligodendrocytes by the JC virus. PML has been described in various immunosuppressed populations including HIV patients, multiple sclerosis patients on monoclonal antibodies, those with hematologic malignancies, and patients with autoimmune diseases on chronic steroids/immunosuppressive agents. In affected HIV patients, mortality from PML is 30% in the first year, [12] while in those with leukemia/lymphoma, prognosis is even worse with 90% of patients dying in the first 2 months. In multiple sclerosis, patients on medications such as natalizumab and less commonly, tecfidera and rituximab, the risk of PML is much higher in patients with positive JC serology when compared to those who are JC negative. Survival rate in these populations has been reported to be 77% after 3 years but those who do survive, usually end up having significant morbidity. Only a small number of survivors (~20%) are thought to have mild-moderate disability after the disease [13]. There is no effective treatment for PML. In HIV patients, HAART is the most appropriate treatment and has led to a decrease in incidence of PML in that population. Immune reconstitution is the best currently available treatment at this point and for patients who are on immunomodulating/immunosuppressive therapies, stopping those medications is the first step. In multiple sclerosis patients on natalizumab, plasma exchange is used to facilitate immune reconstitution by clearing natalizumab from the circulation. Immune reconstitution is difficult to achieve in patients with hematological or solid malignancies which is the primary reason these populations have the worst prognosis. Other medications that have some evidence regarding their effectiveness based on case reports are mirtazapine, cytarabine, and cidofovir but the latter two failed to show any benefit in PML treatment studies [14]. Newer candidate medications include interferons, interleukin 2, interleukin 7, and a CCR5 inhibitor, maraviroc.

## Bacterial Infections

Various bacterial pathogens can also cause CNS infections in immunocompromised individuals manifesting as meningitis, encephalitis, and abscesses. Bacterial meningitis is characterized by fever, headache, confusion, and nuchal rigidity. When suspected, empiric antimicrobial therapy should be instituted immediately (Not waiting for blood and CSF cultures), and blood cultures should be drawn. If safe, lumbar puncture should be attempted and CSF studies typically show neutrophilic pleocytosis with decreased glucose (less than 2/3rd\*\*\* of the serum glucose) and increased protein, with an increased opening pressure. Speciation of the infective pathogen is accomplished through either blood or CSF cultures. Emergence of multi-resistant pathogens complicates management of bacterial infections, even more so in immunocompromised individuals. In immunocompromised patients, especially transplant patients, *Listeria monocytogenes* is a common pathogen and a leading cause of meningoencephalitis, specifically rhombencephalitis. Less common pathogens include *Mycobacterium tuberculosis* and *Nocardia* with the latter more commonly causing abscesses. Contrast enhanced MRI imaging is used to detect abscesses which present as ring enhancing and hyperintense lesions.

In addition to brain abscesses, epidural spinal abscesses may result in severe morbidity and compressive myelopathy [15]. The most common pathogens are Staphylococcus and Streptococcus, followed by Gram-negative bacteria (*Haemophilus*, *E. coli*, *Proteus*, *Pseudomonas*) and mycobacteria (*M. tuberculosis*). The treatment for epidural abscesses includes targeted antibiotic therapy and early surgical intervention when there is concern for neurological involvement [16]. Prognosis is poor in cases with delayed diagnosis/treatment and worse in developing countries. Mortality is thought to range from 6% to 32%.

## Fungal Infections

Fungal microorganisms can cause various CNS manifestations including abscesses, encephalitis, and cerebrovascular infarcts. *Cryptococcus* is the most common fungal opportunistic CNS infection. One half of cryptococcal infections are associated with HIV [17]. The rest of the cases are mostly seen in immunosuppressed and transplant patients, especially with corticosteroid use, with remaining ~15% of cases seen in immunocompetent hosts. Cryptococcal CNS infections are usually characterized by headache, confusion, focal cranial nerve palsies, and seizures. A large number of immunosuppressed patients may not exhibit fever or meningeal signs. They can have meningeal enhancement with associated gyriform T2 hyperintensities on imaging. CSF examination is used for both diagnosis and staging. CSF results are significant for elevated opening pressure, low glucose, elevated protein, and elevated IgG index. There is usually a lymphocytic pleocytosis but cell counts can be low in HIV and immunosuppressed patients. It is also a poor prognostic sign in addition to persistent fungal growth and elevated intracranial pressure. CSF studies including cryptococcal antigen and latex agglutination (India Ink test) are used to further help with diagnosis. Management requires therapy with antifungal medications such as amphotericin B initially with flucytosine. Fungistatic drugs such as fluconazole are used to replace amphotericin B after initial course of treatment to complete a total treatment course

of 12–18 months. Antifungal treatment is combined with steroids to prevent emergence of IRIS but this needs to be balanced to prevent worsening of the cryptococcal infection. IRIS is discussed in more detail later in the chapter. Management of intracranial pressure in the short term can be aided by the use of regular lumbar punctures. Surgical shunting is considered in refractory cases.

*Aspergillus* are septated molds that invade tissue and vasculature in immunosuppressed patients. Aspergillosis is usually associated with pulmonary infections in patients with COPD. However, they can involve the brain and/or become systemic especially in immunocompromised populations. It can cause hemorrhagic infarcts with involvement of the lenticulostriate and thalamogeniculate arteries. They can also form mycotic aneurysms by invading vessel walls and with chronic infection, lead to the development of abscesses and granulomas. Intracranial involvement is seen in 10–20% of patients and formation of mass lesions is more common than meningoencephalitis. Sinuses and lungs are the primary route of infection with fever, headache, cranial nerve palsies, confusion, and seizures common symptoms. There is also vascular involvement that manifests as strokes due to infiltration of the anterior and middle cerebral arteries. *Aspergillus* may also precipitate cavernous sinus thrombosis manifesting as headache, multiple cranial nerve palsies (involvement of III, IV, VI, V1, and V2), orbital pain, ophthalmoplegia, and proptosis which requires urgent neurosurgical involvement. Diagnosis is made through tissue biopsy culture with serum testing for biomarkers such as galactomannan and 1,3 beta D-glucan serving as ancillary tests. CSF sampling is difficult in many cases due to the presence of brain masses and concern for increased intracranial pressure. MRI can show abscess like ring-enhancing lesions and restricted diffusion in cases of ischemic stroke. Voriconazole is the treatment of choice with liposomal amphotericin B, posaconazole, and itraconazole being some of other alternatives. Adjunctive surgery may be needed in some cases. Mortality is high with 1 year survival ranging between 30% and 45%.

Another common fungal microorganism is *Candida* with an increased risk of infection in transplant patients. Opportunistic CNS infections caused by *Candida* species are uncommon and are usually associated with disseminated candidiasis. Neutropenia is associated with an increased risk of disseminated candidiasis in HIV patients. In addition to immunosuppression, extremes of age, indwelling catheters, drug use, and total parenteral nutrition are other risk factors. Clinically, CNS candidiasis may form granulomas or abscesses or have more diffuse leptomeningeal involvement. Less commonly, it can cause basilar artery thrombosis or subarachnoid hemorrhage by forming mycotic aneurysms. CSF studies exhibit a neutrophilic or monocytic pleocytosis with reduced glucose and elevated protein. CSF cultures are frequently negative and blood cultures that determine evidence of candidemia are more helpful in diagnosis. *Candida* also frequently causes candida endophthalmitis, so an ophthalmologic exam can also help with diagnosis. In terms of treatment, *Candida* species are categorized as *C. albicans* versus non-*albicans* species with the former responding to azoles, but not the latter. Amphotericin B is the preferred treatment of choice and while echinocandins (caspofungin, micafungin) are now the initial treatment for disseminated candidemia, they have low CNS penetration and are not ideal when there is CNS involvement.

*Coccidioidomycosis* is a fungal infection usually seen in the southwestern states of the USA but is more common in transplant patients especially in the first year. Pregnancy, use of TNF alpha inhibitors, and AIDS also increase the risk. CNS involvement typically presents as basilar meningitis with white matter/leptomeningeal enhancement in the posterior fossa along with possibility of strokes in the brainstem, cerebellum, and basal ganglia. Hydrocephalus and vasculitis can complicate 40% of these infections months later [17]. CSF studies can reveal an eosinophilic pleocytosis with elevated protein and low glucose. Cultures are only positive in 15% but diagnostic yield of greater than 70% can be achieved by the use of complement fixation titers. Fluconazole is the drug of choice and lifelong treatment may be needed due to risk of relapse, with mortality still high at 40%.

*Mucormycosis* is caused by aseptate molds that commonly affect diabetics and other immunocompromised patients. Other risk factors include IV drug use and iron overload conditions include desferrioxamine chelation for treatment of those conditions. The major CNS clinical manifestation is cerebral disease through spread from the sinuses with extension into the orbit and cavernous sinus before reaching the brain through the orbital apex or cribriform plate. Clinically it presents with symptoms of sinusitis, facial pain/numbness, and cranial nerve palsies. It can also involve vascular structures causing infarction and necrosis. MRI imaging might show cavernous sinus and intradural involvement with tissue biopsy culture the gold standard for diagnosis. Treatment includes surgical debridement and high dose liposomal amphotericin B based medication regimens. Mortality from mucormycosis amounts to 25–40%.

### Parasitic CNS Infections

*Toxoplasmosis* is the most common parasitic CNS infection seen in immunosuppressed patients and in transplant patients is usually seen 3 months after transplantation. It usually presents clinically as encephalitis and can present in two different imaging patterns on MRI. The classic MRI pattern includes hyperintensities on T2-weighted with associated edema and ring enhancement, or alternatively consists of multiple areas of hyperintensity on T2-weighted imaging but without contrast enhancement. Diagnosis is established by the demonstration of organisms in blood, tissue, or body fluids. PCR for protozoal organisms can be a useful ancillary test. [18] Treatment is usually with pyrimethamine/sulfadiazine with trimethoprim/sulfamethoxazole used for prophylaxis and also potentially as an alternative treatment agent.

Other parasites that can cause opportunistic CNS infections include different amebic organisms with MRI showing multiple areas of punctate or ring-enhancing lesions. These infections are fortunately rare, but are associated with a dismal prognosis [19]. Additionally, endemic exposure to other parasites may also lead to opportunistic CNS infections [3].

### Immune Reconstitution Inflammatory Syndrome

First recognized in HIV patients after the advent of highly active antiretroviral therapy (HAART), there is an emergence of an inflammatory response which leads to

clinical worsening as opposed to improvement. Inflammatory response occurs in the context of re-emergence of the immune system as viral loads fall and CD4 T lymphocytes increase, and has been named immune reconstitution inflammatory syndrome (IRIS). IRIS typically manifests a few months after the initiation of therapy in HIV patients, and has been described in 9–47% of AIDS patients [20]. In addition to HIV patients, this pattern can be seen in other immunocompromised patients who develop other infections such as progressive multifocal leukoencephalopathy (PML) or cryptococcal meningitis [21]. IRIS is more likely to develop when the underlying immunodeficiency is severe and/or long in duration. The inflammatory response can be seen when immune reconstitution occurs as part of treatment for a clinically active pathogen or less commonly, while the pathogen is still clinically asymptomatic. In the former, this leads to worsening of symptoms from the opportunistic infection as a result of the inflammation while in the latter, immune reconstitution can lead to activation of the latent pathogen.

In patients with PML, IRIS leads to transformation of PML lesions with involvement of lymphocyte infiltration and breakdown of the blood brain barrier. This manifests as contrast enhancement and cytotoxic edema on MRI imaging. While development of an effective immune response can improve survival in PML patients by controlling the JC infection, it also can lead to more widespread tissue destruction and brain herniation. On imaging, contrast enhancement can be suggestive of IRIS but its absence does not rule out its presence. In patients with natalizumab associated PML, image showing associated punctate or linear enhancement is consistent with history of IRIS and might be an early manifestation of this condition [21]. Management of IRIS is usually accomplished by treatment with high dose corticosteroid therapy (1 g of methylprednisolone for 3–5 days) that might be repeated every few weeks depending on clinical progression. This treatment is usually started after the development of immune reconstitution. Another medication that has been used in IRIS is maraviroc which inhibits CCR5 mediated inflammation and has been used in patients with natalizumab associated PML.

In patients with cryptococcal meningitis, there is a risk of developing IRIS with treatment especially in patients who have co-existing HIV and are treated with HIV therapy and cryptococcal meningitis treatment at the same time. In HIV patients, HAART treatment that is delayed for 4–5 weeks after treatment of cryptococcal meningitis leads to more favorable outcomes. Since, a significant portion of the immune response in cryptococcal meningitis is thought to be secondary to the polysaccharide capsule, routine treatments of associated IRIS include large volume of lumbar punctures and steroids if needed.

## **Posterior Reversible Encephalopathy Syndrome**

Posterior reversible encephalopathy syndrome (PRES) is an important neurological emergency with specific imaging pattern which includes bilateral white matter hyperintensities preferentially involving the posterior circulation, with vasogenic edema and typically is followed by complete clinical and radiographic resolution



[22]. Common symptoms include headaches, blurry vision, confusion, akinetic mutism, and seizures. PRES is often associated with neurotoxicity of calcineurin inhibitors (cyclosporine, tacrolimus), but may infrequently present with other immunosuppressants [23, 24]. PRES usually occurs within a month after initiation of calcineurin inhibitors when higher dosage and intravenous preparations may be used, but may also arise once patients have been on the medications for more than a year. While toxic levels of these medications might increase the risk of PRES, they are not required for its development [25]. PRES usually improves upon reducing the dose or switching the immunosuppressant, and this has to be balanced with the risk of rejection in transplant patients [26]. Co-existing hypertension and electrolyte disturbances might increase the risk of PRES in transplant patients [25]. Pathophysiology of PRES is not well understood, and it is also unclear why there is usually a preference for posterior circulation with the leading theory being the less extensive sympathetic innervation in that area. Other areas that can be involved are brainstem, cerebellum, thalamus, basal ganglia, and bilateral frontal lobes. Withdrawal of the offending medication usually leads to resolution of symptoms; however, neuroimaging findings trail behind clinical symptoms for weeks to months. A minority of patients develop irreversible ischemic changes with cytotoxic edema and restricted diffusion on MRI imaging [22]. Contrast enhancement is also rare but might be seen in a minority of patients and could be related to the timing of imaging in relation to symptom onset.

## Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a demyelinating disease most commonly affecting brainstem in patients with alcoholism, liver cirrhosis, malnourishment, and often with overtreatment of serum hyponatremia or less commonly hypernatremia. Less commonly, demyelination extends beyond pons (extrapontine myelinolysis) typically involving basal ganglia and grey–white matter junction. In immunosuppressed patients, it is typically seen with AIDS and in the transplant population (especially after liver transplantation). CPM has been described in up to 1–8% of liver allograft recipients, [26] and typical imaging presentation of trident T1 hypointense and T2 hyperintense lesions in the central pons can lag behind clinical symptoms or may be an incidental finding in asymptomatic patients. While CPM is often attributed to an overly rapid correction of hyponatremia, other patients may develop CPM without predisposing risk factors. Typical clinical findings include quadriparesis, dysphagia, and decreased responsiveness [27]. Prevention of CPM with careful electrolyte management is vital because there is still no known effective treatment.

## Stroke

Clinically, cerebrovascular disorders present and are treated similarly in immunosuppressed individuals as in general population. Immunosuppressed patients are at

an increased risk of both ischemic and hemorrhagic strokes. Ischemic strokes are especially common in heart transplant, kidney transplant and there is also an increased risk in HIV patients [28–30]. Ischemic strokes in transplant patients are often related to the surgical procedure of transplantation, infections such as vasoinvasive fungal infections (e.g., aspergillosis) and accelerated atherosclerosis with the first two usually causing early onset strokes while the latter responsible for more subacute-chronic strokes. Hemorrhagic strokes in liver transplant patients are thought to be secondary to metabolic or infectious causes. Metabolic causes include coagulopathy and thrombocytopenia while fungal vasoinvasive infections and mycotic aneurysms caused by endocarditis are common infectious etiologies. *Aspergillus* may also precipitate cerebral venous thrombosis.

## Epilepsy

Seizures are a common symptom in transplant recipients and other immunosuppressed patients, and occur either secondary to the development of opportunistic CNS infections, drug toxicities, metabolic disturbances or due to the development of PRES. Status epilepticus is treated similarly to status epilepticus in other patients, while choice and dosing of maintenance antiepileptic medications will also depend on their potential for interaction with immunosuppressant medications [31].

---

## Conclusion

Neurologic complications and emergencies in immunocompromised patients have wide spectrum and clinical manifestations will depend on underlying medical conditions leading to immunodeficiencies (e.g., HIV, antirejection medications), comorbidities, extent of immunosuppression, environmental exposures to infectious agents, and various medications used in these patients. Opportunistic CNS infections may have an insidious onset and we have to maintain our alertness as delayed diagnosis may result in significant morbidity.

---

## References

1. Linden PK. Approach to the immunocompromised host with infection in the intensive care unit. *Infect Dis Clin N Am*. 2009;23(3):535–56.
2. Sakhuja V, Sud K, Kalra OP, D'Cruz S, Kohli HS, Jha V, et al. Central nervous system complications in renal transplant recipients in a tropical environment. *J Neurol Sci*. 2001;183(1):89–93.
3. Walker M, Kublin JG, Zunt JR. Parasitic central nervous system infections in immunocompromised hosts: malaria, microsporidiosis, leishmaniasis, and African trypanosomiasis. *Clin Infect Dis*. 2006;42(1):115–25.
4. Fishman JA. Infections in immunocompromised hosts and organ transplant recipients: essentials. *Liver Transpl*. 2011;17(Suppl 3):S34–7.
5. van de Beek D, Kremers W, Daly RC, Edwards BS, Clavell AL, McGregor CG, et al. Effect of neurologic complications on outcome after heart transplant. *Arch Neurol*. 2008;65(2):226–31.



6. Zivkovic SA, Abdel-Hamid H. Neurologic manifestations of transplant complications. *Neuro Clin.* 2010;28(1):235–51.
7. Whitley RJ. Herpes simplex virus infections of the central nervous system. *Continuum.* 2015;21(6, Neuroinfectious Disease):1704–13.
8. Leypoldt F, Titulaer MJ, Aguilar E, Walther J, Bonstrup M, Havemeister S, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology.* 2013;81(18):1637–9.
9. Nagel MA, Gilden D. Neurological complications of varicella zoster virus reactivation. *Curr Opin Neurol.* 2014;27(3):356–60.
10. Yango AF, Fischbach BV, Levy M, Chandrakantan A, Tan V, Spak C, et al. West Nile virus infection in kidney and pancreas transplant recipients in the Dallas-Fort Worth Metroplex during the 2012 Texas epidemic. *Transplantation.* 2014;97(9):953–7.
11. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med.* 2012;366(20):1870–80.
12. Khanna N, Elzi L, Mueller NJ, Garzoni C, Cavassini M, Fux CA, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. *Clin Infect Dis.* 2009;48(10):1459–66.
13. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukoencephalopathy C. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord.* 2015;8(6):255–73.
14. De Luca A, Ammassari A, Pezzotti P, Cinque P, Gasnault J, Berenguer J, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS.* 2008;22(14):1759–67.
15. Reihnsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. *Neurosurg Rev.* 2000;23(4):175–204; discussion 5.
16. Pradilla G, Ardila GP, Hsu W, Rigamonti D. Epidural abscesses of the CNS. *Lancet Neurol.* 2009;8(3):292–300.
17. Panackal AA, Williamson PR. Fungal infections of the central nervous system. *Continuum.* 2015;21(6, Neuroinfectious Disease):1662–78.
18. Pustavoitau A, Bhardwaj A, Stevens R. Neurological complications of transplantation. *J Intensive Care Med.* 2011;26(4):209–22.
19. Mendez O, Kanal E, Abu-Elmagd KM, McFadden K, Thomas S, Bond G, et al. Granulomatous amebic encephalitis in a multivisceral transplant recipient. *Eur J Neurol.* 2006;13(3):292–5.
20. Bahr N, Boulware DR, Marais S, Scriven J, Wilkinson RJ, Meintjes G. Central nervous system immune reconstitution inflammatory syndrome. *Curr Infect Dis Rep.* 2013;15(6):583–93.
21. Clifford DB. Neurological immune reconstitution inflammatory response: riding the tide of immune recovery. *Curr Opin Neurol.* 2015;28(3):295–301.
22. Lee VH, Wijedicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Arch Neurol.* 2008;65(2):205–10.
23. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology.* 2007;68(23):2039–40.
24. Small SL, Fukui MB, Bramblett GT, Eidelman BH. Immunosuppression-induced leukoencephalopathy from tacrolimus (FK506). *Ann Neurol.* 1996;40(4):575–80.
25. Lamy C, Oppenheim C, Meder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging.* 2004;14(2):89–96.
26. Guarino M, Benito-Leon J, Decruyenaere J, Schmutzhard E, Weissenborn K, Stracciari A. EFNS guidelines on management of neurological problems in liver transplantation. *Eur J Neurol.* 2006;13(1):2–9.
27. Graff-Radford J, Fugate JE, Kaufmann TJ, Mandrekar JN, Rabinstein AA. Clinical and radiologic correlations of central pontine myelinolysis syndrome. *Mayo Clin Proc.* 2011;86(11):1063–7.

28. Chow FC. HIV infection, vascular disease, and stroke. *Semin Neurol.* 2014;34(1):35–46.
29. Jarquin-Valdivia AA, Wijdicks EF, McGregor C. Neurologic complications following heart transplantation in the modern era: decreased incidence, but postoperative stroke remains prevalent. *Transplant Proc.* 1999;31(5):2161–2.
30. Oliveras A, Roquer J, Puig JM, Rodriguez A, Mir M, Orfila MA, et al. Stroke in renal transplant recipients: epidemiology, predictive risk factors and outcome. *Clin Transpl.* 2003;17(1):1–8.
31. Shepard PW, St Louis EK. Seizure treatment in transplant patients. *Curr Treat Options Neurol.* 2012;14(4):332–47.

# Neurological Emergencies in Pregnancy

# 8

Sucharita Ray, Rohit Bhatia, and Mamta Bhushan Singh

---

## Introduction

Significant physiological changes occur in a woman's body during pregnancy. Several disease conditions are known to have marked exacerbations as well as abatement during pregnancy owing to these changes occurring in the body. The pathophysiologic mechanisms for exacerbation can be secondary to pregnancy itself or may occur due to a completely unrelated mechanism. It is of extreme importance to understand the pathophysiologic mechanism and behavior of each of these disease conditions to ensure timely treatment and reduce morbidity and mortality of both mother and child. Here we focus on the neurological conditions with acute aggravations during pregnancy as well as primarily non-neurological conditions with a significant neurologic complication which may occur in pregnancy and discuss their modes of presentations, pathophysiologic basis, treatment, etc. The condition of cerebral venous thrombosis is dealt with in detail elsewhere in this book and hence will not be covered in this chapter.

---

## Pathophysiology of Neurological Changes in Pregnancy

The secretion of maternal hormones by the ovary followed by the placenta brings about a plethora of changes in maternal hemodynamics and hemostatic functions. Apart from the 45% increase in the plasma volume and 25% increase in red blood cell mass, there also occurs physiologic anemia and reduced peripheral resistance. Resting heart rate and stroke volume see a rise up to 25% each. The increase in

---

S. Ray

Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

R. Bhatia (✉) · M. B. Singh

Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

fibrinogen and plasma clotting factors also lead to a systemic hypercoagulable state but a concurrent accelerated thrombolytic state also coexists with increased concentrations of antithrombin III, plasminogen, and fibrin degradation products [1]. Such dramatic changes occurring as a normal physiological process can lead to multiple conditions by their excesses or deficiencies. In addition, various disease processes interact differently with this enhanced physiological state and lead to different diseases, as we shall discuss below.

**Classification of Neurological Diseases Which Can Present as Emergencies in Pregnancy**

Several conditions can present first time to the Neurological Emergency. Complications of diseases present in the non-pregnant state can also present for the first time during pregnancy. It is helpful to remember a brief classification of these conditions and their emergent neurological manifestations during pregnancy (Table 8.1).

**Hematoneurologic Emergencies in Pregnancy**

**Hemolysis Elevated Liver Enzymes Low Platelets (HELLP) Syndrome**

It is a rare complication that occurs in up to 0.5–0.9% in all pregnancies. About 70% of cases develop before delivery, mostly within 27th and 37th gestational weeks and the remainder occurs within 48 h after delivery. It occurs as a variant of severe pre-eclampsia during pregnancy. Originally described by Weinstein in 1982, it consists of a triad of hemolysis, elevated liver enzymes, and thrombocytopenia [2]. It is associated with pre-eclampsia in up to 90% and occurs in the second trimester or also in the postpartum. Neurological complications associated with HELLP

**Table 8.1** Neurological emergencies in pregnancy

Hematoneurologic syndrome	Hemolysis elevated liver enzymes and low platelets syndrome (HELLP syndrome), Acute leukemias
Neuroinfectious conditions:	Bacterial, viral, fungal meningitis and encephalitis Toxoplasma rubella cytomegalovirus, herpes virus (TORCH) group of infections
Posterior reversible encephalopathy syndrome (PRES)	
Status epilepticus (SE) in pregnancy	
Cerebrovascular conditions in pregnancy	Ischemic stroke Hemorrhagic stroke Subarachnoid hemorrhage Cerebral venous thrombosis (CVT)
Primary obstetrics causes	Pre-eclampsia Eclampsia

syndrome were seen in up to 66% of all patients with HELLP syndrome and account for a large proportion of the mortality [3].

Approximately 30–60% of the women may have headache and about 20% have visual symptoms. The complications took the form of seizures, focal neurological deficits, and encephalopathy. Neuroimaging revealed features suggestive of posterior reversible encephalopathy syndrome (PRES) with or without associated intracranial hemorrhage [4]. The mean term of delivery is 32 weeks and rapid termination of pregnancy by vaginal delivery or by cesarean is generally recommended as soon as fetal lung maturity is obtained [5]. Expectant management is done in patients with a gestation period of 27 weeks or less and requires close maternal and fetal surveillance with provisions for undertaking immediate cesarean section if risks increase for developing maternal or fetal complications (*abruptio placentae*, acute renal failure, pulmonary edema, DIC, perinatal and maternal death) [6]. The development of neurological symptoms usually antedates a worse outcome and hence requires urgent terminative procedures to minimize fetal and maternal complications.

## Neurological Emergencies of Leukemia

Leukemias and lymphomas are devastating clinical conditions that can result in neurological complications either due to the direct infiltration of leukemic cells or due to medications or immunosuppressed state. Opportunistic infections can also cause catastrophic conditions in the diseased. The neurological complications that can occur in acute lymphoblastic leukemia (ALL) include cerebrovascular accidents and convulsions. Leukoencephalopathy and neurocognitive deficits can develop after completion of chemotherapy for ALL. Leukemic meningitis, as well as *Aspergillus* meningitis, herpes zoster encephalitis, etc. can develop due to immunosuppressed state [7, 8]. Moreover metastatic and paraneoplastic complications can also occur in leukemias with catastrophic presentations [9]. Malignancy can complicate pregnancy in up to one per thousand pregnancies [10]. The four most common malignancies to complicate pregnancy include cervical and breast cancer, malignant melanoma, and lymphoma [11]. Myeloproliferative neoplasms are more commonly encountered in pregnancy owing to the rising median age at pregnancy, improved diagnosing techniques. On the other hand, myelodysplastic syndromes and chronic lymphoblastic leukemia generally occur at an older age and are rarely diagnosed during pregnancy [10, 12] (Table 8.2).

---

## Management of Neurological Complications of Malignancy in Pregnancy

Treatment of malignancy as such requires special precautions depending on the stage of pregnancy. Many medications like all-trans-retinoic acid, cytarabine, daunorubicin, methotrexate, etc. are contraindicated in the first trimester due to the potential for causing severe teratogenic effects [13]. Many physicians

**Table 8.2** Acute neurological conditions associated with leukemias

<i>Acute meningitis</i>
Leukemic
Infectious conditions: bacterial, fungal, chemical (drug induced)
<i>Parenchymal hemorrhage</i>
L-Asparaginase induced sinus thrombosis, chemotherapy-induced thrombocytopenia, Moyamoya disease, disseminated intravascular coagulation (DIC), fungal mycotic aneurysm
<i>Encephalopathy</i>
Radiation-related, methotrexate-induced, toxic, metabolic, posterior reversible encephalopathy (PRES)
<i>Multiple cranial nerve palsies</i>
<i>Epidural hemorrhage</i>
<i>Status epilepticus (SE)</i>
<i>Spinal cord compression</i>
<i>Radiculopathy</i>

recommend termination of the fetus in the first trimester or even up to 20 weeks in case of acute lymphoblastic leukemia followed by the institution of conventional therapy [14]. The emergent neurological complications arising in these malignancies need management as mandated with special attention to the malignant state or consequence of chemotherapy. Chemotherapeutic drugs can have a serious effect on the hematological profile of the patient. For example, L-Asparaginase can induce a sinus thrombosis, chemotherapy can cause thrombocytopenia. Promyelocytic leukemia can cause disseminated intravascular coagulation. Neurological complications can all arise from this disturbance in the hematological milieu.

## Nervous System Infections in Pregnancy

The anatomic separation between the mother and the fetus, prevention of antigenic presentation, and maternal immune suppression are some of the factors that put the pregnant woman at risk for infectious diseases. The pattern of diseases seen in pregnancy is not typical for immunocompetent patients but rather reflects the pattern seen in patients with impaired cell-mediated immunity.

### Bacterial Meningitis

Per se pregnancy does not increase the risk for bacterial meningitis except for infection with *Listeria monocytogenes* (*L. monocytogenes*), which has been reported to be nearly 20 times more common in pregnancy than in the general population. The reason for this is the intracellular life cycle of *L. monocytogenes* which allows it to cross the placental and blood–brain barrier [15]. Most of the infections with *Listeria* are mild and asymptomatic although 20% of cases may result in spontaneous

abortion or stillbirth. It can cause both meningitis or meningoencephalitis with fever, headache, or impaired consciousness ranging from lethargy to coma. While nuchal rigidity may be less common, infection with *Listeria* may affect the brainstem causing rhombencephalitis presenting with cranial nerve deficits, ataxia, hemiparesis, and respiratory failure. Diagnosis of *Listeria* is by culture of the organism from blood, amniotic fluid, or cerebrospinal fluid. Treatment of choice for *Listeria* infection in pregnancy is ampicillin 2 g every 4 h or trimethoprim-sulfamethoxazole in allergic patients. Duration of treatment is 3 weeks for meningitis and 6–8 weeks for encephalitis [16].

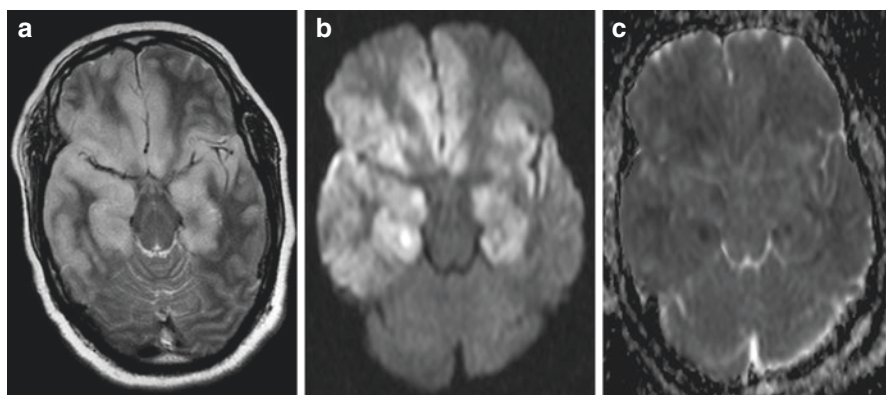
Among the agents causing community-acquired meningitis (*Streptococcus pneumoniae* and *Neisseria meningitidis*) pregnant women are at similar risk of developing meningitis from these agents as the general population [17]. Despite treatment mortality from pneumococcal meningitis is reported as 19–34% and about 3–13% for meningococcal meningitis [18]. Neonatal outcomes are uniformly more dismal showing approximately 47% rate of stillbirth, abortion, or neonatal death [19]. Empirical therapy for community-acquired bacterial meningitis includes dexamethasone, a third- or fourth-generation cephalosporin and vancomycin [20].

### ***Cryptococcus neoformans* Meningitis**

Pregnancy with cryptococcal meningitis presents with severe symptoms and signs. Papilledema is present in 50% of cases whereas fever maybe seen in up to 33% and altered mental status and or vision in up to 44%. Diagnosis relies on antigen positivity and culture as well as direct visualization of encapsulated forms of *Cryptococcus neoformans* in India ink smears of CSF. First-line management consists of amphotericin B with flucytosine. After delivery, the woman should be switched to fluconazole and advised to avoid breastfeeding. Teratogenic potential or other toxic side effects on the fetus have not been established for amphotericin B [21].

### **Herpesviridae Group of Infections**

The herpesviridae are a group of DNA viruses of which the herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus (VZV), and cytomegalovirus (CMV) are known to cause various diseases in humans (Fig. 8.1). The pregnant state usually begets a more severe and disseminated form of the disease. However, the number of pregnant women who acquire HSV-1 or HSV-2 infection during pregnancy has been calculated to be merely 0.5–2%. Varicella infection, pegged to occur with a frequency of about 1/1000 pregnancies, is more severe in intensity than in non-pregnant women. Prevention with Varicella Zoster immunoglobulin is contraindicated in pregnancy. Chances of primary HSV infection in pregnancy are rare although mortality of such cases may approach nearly 50%.



**Fig. 8.1** Herpes encephalitis. Lesions involving bilateral temporal lobes including hippocampi, basifrontal regions show cortical thickening and high signal intensity on T<sub>2</sub>-WI (a). Lesions show evidence of restricted diffusion on DWI (b). Images and ADC maps (c)

Primary genital HSV infection is the most common type of HSV infection occurring in pregnancy. Gingivostomatitis and vulvovaginitis herpetica tend to disseminate more and cause encephalitis [22].

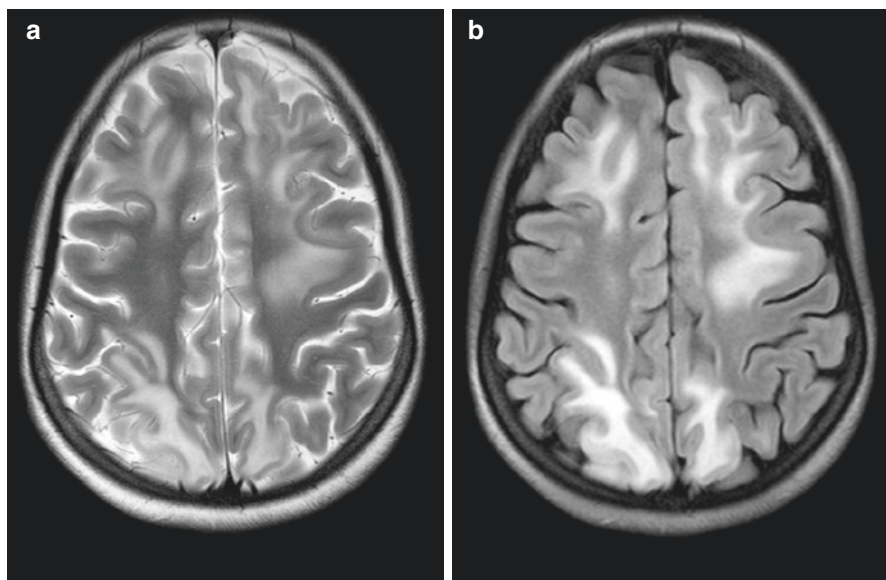
## TORCH Group of Infections

The forms of cytomegalovirus (CMV) infection and toxoplasmosis in the pregnant woman are typically asymptomatic. However, owing to its large range of symptoms in the unborn fetus it mandates treatment. Latent toxoplasmosis has been linked not only to the pathology of several psychiatric and chronic neurological conditions but also to being a cause for cryptogenic epilepsy [23].

## PRES in Pregnancy

Posterior reversible encephalopathy syndrome (PRES) is an under diagnosed clinico-neuroradiological emergency that can complicate pregnancy. Described initially in 1996 by Hinchey et al. it has been associated with several common clinical conditions like hypertensive encephalopathy, renal failure, autoimmune conditions, and administration with immunosuppressants or cytotoxic agents [24]. Cyclosporine, tacrolimus, granulocyte colony-stimulating factor, cisplatin, epoetin, and immune globulin are some of the common offenders [25]. The clinical syndrome is usually recognized by headache, altered mental status, multiple seizures, and vision loss [26]. Visual complications can be severe with hypertensive retinopathy, exudative retinal detachment, and cortical blindness being the most common causes. Blindness is mostly caused due to the preferential occipital lobe



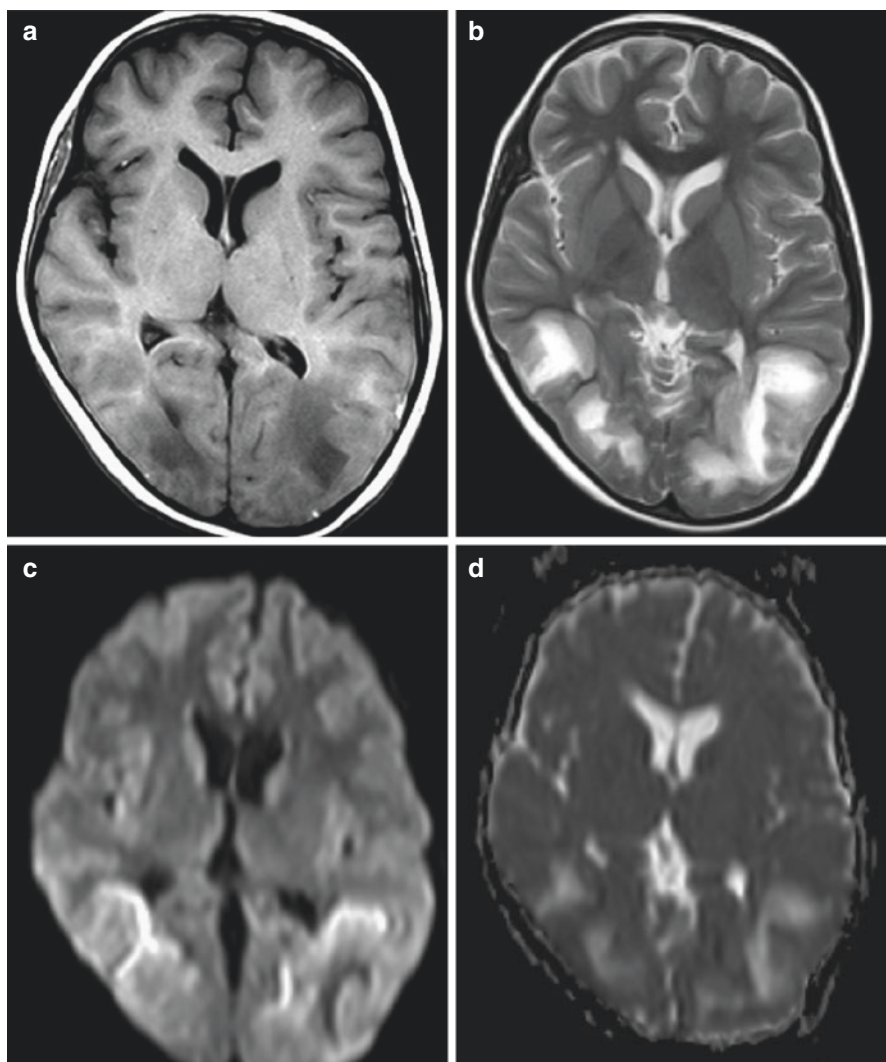


**Fig. 8.2** MRI scan in a patient with PRES. T2W (a) and FLAIR (b) image reveal white matter hyperintensities posteriorly and anteriorly

involvement and is reversible within 4 h to 8 days (Figs. 8.2 and 8.3) [27]. Intracranial hemorrhage is the most devastating consequence of this condition and increases morbidity and mortality [28].

Vasogenic edema due to disruption in the cerebral autoregulatory mechanisms leads to disruption in the blood–brain barrier. This increased perfusion pressure leads to extravasation of fluid, macromolecules, and even red blood cells causing the neurological manifestations. (Hinchey) Regions of the brain supplied by the anterior circulation have better sympathetic innervation as compared to the posterior circulation. Symptoms can develop in hours and up to 70% of the people are hypertensives [29]. Neuroimaging findings largely echo the anatomical distribution. Non-contrast CT scans show bilateral symmetrical hypodensities of white matter typically in the parieto-occipital region. Magnetic resonance imaging also shows high signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [30].

Management consists of an optimized use of anti-hypertensives along with the removal of offending agents. Intravenous magnesium therapy is a good treatment option for the treatment of both hypertension and clinical seizures if any. Currently accepted paradigm of treatments stresses on a timely and aggressive control in an intensive care setting. Patients with an obstetric cause for PRES have a better outcome. Despite proper management, marked functional impairment was seen in 44% whereas mortality was seen in nearly 16% of cases [31].



**Fig. 8.3** PRES. MRI scan. Signal abnormalities are seen bilaterally in the parieto-occipital region. These appear iso-hyperintense on T<sub>1</sub>- (a), hyperintense on T<sub>2</sub>-WI (b), and show a mixed pattern of restricted and increased diffusion on DWI (c), and ADC maps (d)

### Status Epilepticus (SE) in Pregnancy

Whereas pregnancy in a woman with epilepsy is not contraindicated, definite risks owing to the pregnant state exist and occasionally complications may arise due to change in blood levels of antiepileptics due to pregnancy as well as an increase in seizure frequency due to the pregnant state per se. Poor compliance to antiepileptic medications is responsible for nearly 27% of the cases of SE in pregnancy [32]. The most common and

prevalent neurological emergency associated with pregnancy is, without a doubt, the onset of SE. Increased frequency of seizures is reported in nearly 37% of the pregnancies [33]. Pregnancy-related SE complicates pregnancy in only about 0.6% of the cases. However, its management is of special concern due to the risk imposed on both the mother and the child with almost 28.5% mortality at discharge [34]. Spontaneous abortions have been noted in 8.4% and stillbirths seen in 0.6% of the EURAP registry [35].

SE is said to be pregnancy-related when it develops during pregnancy and within 6 months after delivery. Other causes like irregular or suboptimal drug intake in pre-existent epilepsy, vasculitis, vitamin B6 deficiency, cavernous angiomas, herpes encephalitis, reversible cerebral vasoconstriction syndrome (RCVS). Hepatic porphyria, limbic encephalitis, and cortical venous sinus thrombosis have been found to be some of the precipitating factors for status epilepticus in pregnancy. Eclampsia is usually not included as a cause of SE related to pregnancy.

For these patients, aggressive management is the key to reaching a diagnosis and should be carried out without delay. Cerebrospinal fluid analysis is of paramount importance. Raised protein levels with preserved sugars and mild or no pleocytosis can hint at the possibility of a viral infection. Serology can also be performed for ruling out the presence of N-methyl-D-aspartate receptor antibodies, infection with herpes simplex virus, etc. Radiological correlation with MRI can point out to the presence of superior sagittal sinus thrombosis with venous infarction but findings may also be the same as any other person with epilepsy [36].

Treatment of patients with SE in pregnancy should focus on immediate seizure control. General anesthesia should be introduced promptly when AEDs fail. Specific conditions like lupus mandate the judicious use of anticoagulants and immunosuppressants. Azathioprine and corticosteroids are considered to be relatively safe with reduced risk of teratogenicity to the fetus [37]. Prolonged SE can reduce placental blood flow and induce fetal hypoxia and hence necessitate an emergency termination of pregnancy. In addition, prevention of preventable precipitants of seizures such as drug level fluctuations should be ensured with therapeutic drug monitoring and ensuring compliance among people not taking the medicine.

---

## Cerebrovascular Accidents in Pregnancy

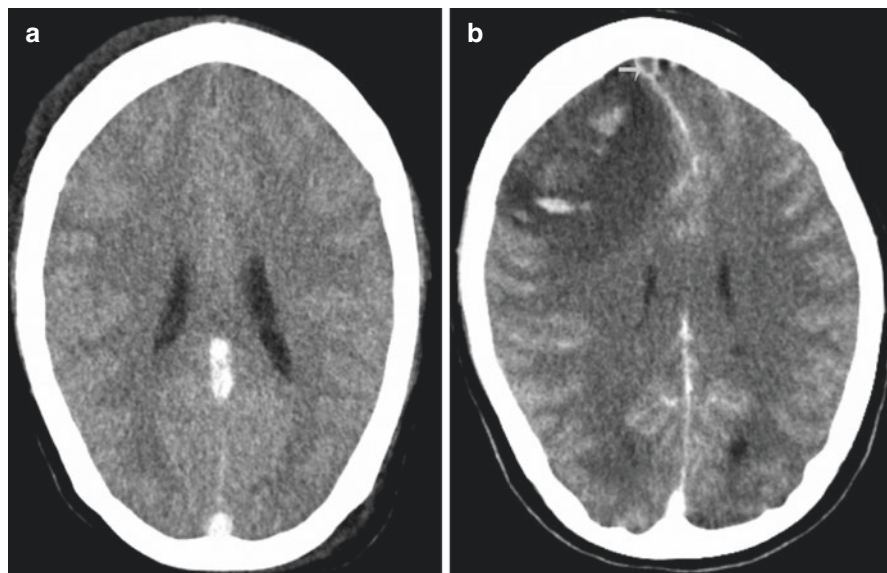
Cerebrovascular accident is perhaps the most dramatic of all neurological emergencies which can present in pregnancy and can occur up to three times more as compared to the non-pregnant state [38]. As a neurological condition, it manifests with more severity and has worse outcomes compared to men. Stroke complicating pregnancies can be both ischemic and hemorrhagic in nature. Its incidence has been reported to vary between 11 and 26 deliveries per 100,000 [39]. The etiology for hemorrhagic stroke includes vascular anomaly, pre-eclampsia/eclampsia, coagulopathy, and a host of undetermined causes. Similarly, the most common causes of cerebral infarction are cardioembolism, cerebral venous thrombosis (CVT), and pre-eclampsia/eclampsia. Conditions unique to pregnancy causing stroke are pre-eclampsia and eclampsia, amniotic fluid embolus, postpartum angiopathy, and peripartum cardiomyopathy. Choriocarcinoma, amniotic fluid embolism, and

paradoxical embolism are some of the rarer causes in pregnancy which may have a stroke-like presentation. In addition, some general causes of stroke in young women, such as carotid and vertebral artery dissection, cerebral vasculitis, migraine, moyamoya disease, and sickle cell anemia can also cause strokes. Advancing maternal age, obesity, and use of contraceptives are also giving rise to an increasing number of traditional causes for strokes. Mortality rates vary between 10% and 13% and are disproportionately higher in black women, older patients, and in those with no prenatal care [40]. Pregnancy-related ICH has the highest mortality of all varieties of stroke with an in-hospital mortality rate of 20.3% [41, 42].

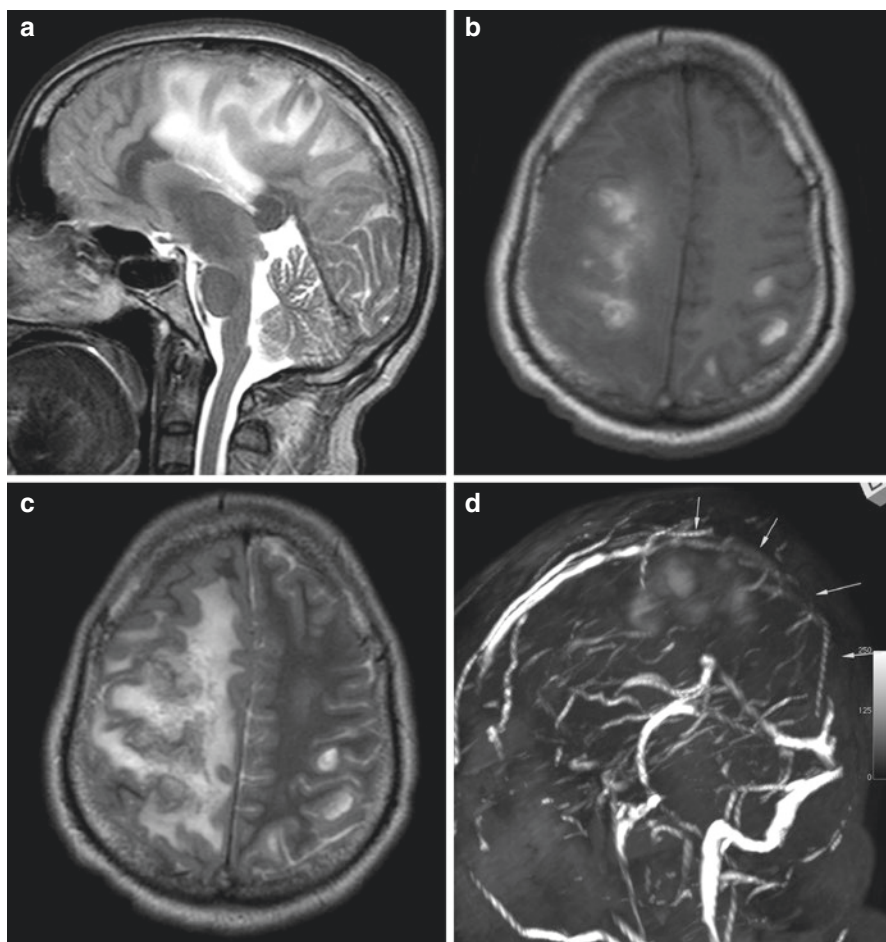
A nation-wide in-patient sample from 2000 to 2001 found an overall incidence of 34.2 strokes per 100,000 deliveries, which compared with an incidence of 10.7 strokes per 100,000 woman-years among non-pregnant women of comparable age showed a three-fold increase in pregnancy. Among all age groups of pregnant women, the rate of hemorrhage was higher in the postpartum period than the antepartum period of the control group [43].

### Cerebral Venous Thrombosis (CVT): (For Details, Also See Chap. 13)

Cerebral sino-venous thrombosis (CVT) represents approximately only 2% of pregnancy-related strokes, occurring with an incidence of approximately 12 per 100,000 deliveries (Figs. 8.4, 8.5, and 8.6). The highest risk period for CVT is third trimester and postpartum, similar to the time frame for risk of venous thromboembolic



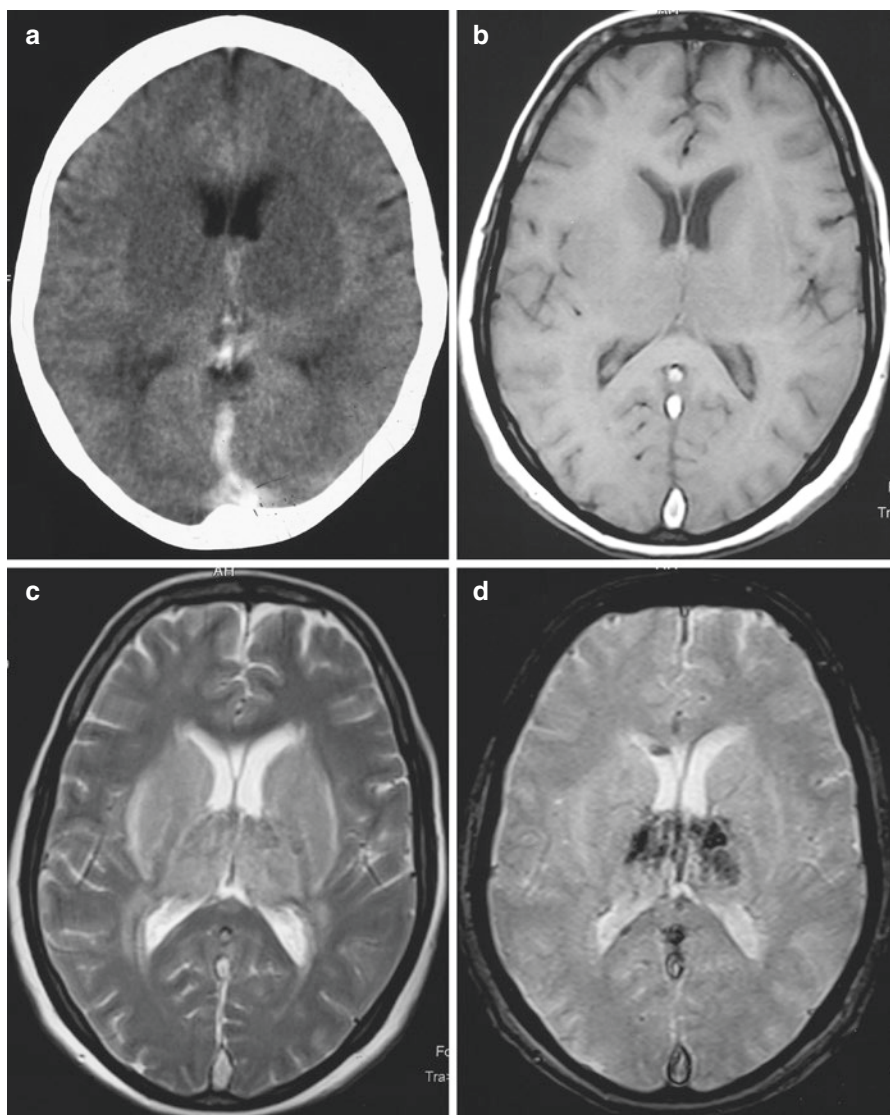
**Fig. 8.4** Cerebral venous thrombosis. NCCT (a) shows a hyperdense straight sinus (white arrow) and superior sagittal sinus (black arrow) suggesting thrombosis. Another case of right frontal venous infarct in the superior sagittal sinus. CECT (b) shows a filling defect (small arrow) within the anterior superior sagittal sinus (empty delta sign)



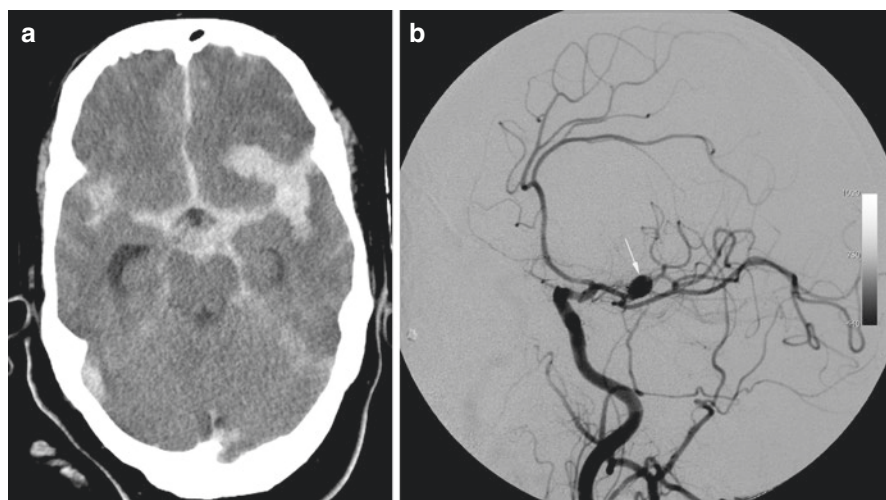
**Fig. 8.5** Superior sagittal sinus thrombosis. Sagittal T<sub>2</sub>-WI (a), axial T<sub>1</sub>- (b), and axial T<sub>2</sub>-WI (c) show loss of flow-void in the superior sagittal sinus and venous infarcts in bilateral frontoparietal lobes. ToF-MRV (d) shows non-visualization of the posterior superior sagittal sinus (arrows) confirming thrombosis

events. Multiple etiologies may be responsible for the same out of which a few are reversible. In women, among other causes, use of oral contraceptives, autoimmune diseases, prothrombotic conditions, pregnancy, intercurrent infection and dehydration, etc., maybe the potential causes [44]. Whereas medical management with anticoagulants is the treatment of choice for managing these conditions, cases with a low Glasgow coma scale score at presentation, large infarct on computed tomography, the presence of mass effect or midline shift, clinical and radiological signs of transtentorial herniation, or deterioration of sensorium despite conservative management may mandate surgical intervention. Decompressive hemicraniectomy is a life-saving procedure under these circumstances [45]. A detailed review of this common and potentially fatal condition has been given in detail in Chap. 13.





**Fig. 8.6** Deep venous sinus thrombosis. Signal abnormalities are seen in bilateral basal ganglia and thalami which appear hypointense on CT (a), hypointense on T<sub>1</sub>-WI (b), and hyperintense on T<sub>2</sub>-WI (c) with evidence of hemorrhage in T<sub>2</sub>-gradient images (d). Both internal cerebral veins (short black arrows) and straight sinus (long black arrows) appear hyperintense on NCCT (a) and hyperintense on T<sub>1</sub>- (b) and T<sub>2</sub>-WI (c) suggesting acute thrombosis



**Fig. 8.7** SAH. NCCT shows (a) diffuse hyperdensity in the basal and Sylvian cisterns suggestive of SAH. DSA (b) shows a left MCA bifurcation aneurysm (white arrow)

### Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage occurs to a greater extent in women than in men and numerous hormonal factors seem to be responsible for the same (Fig. 8.7). Pregnancy is a recognized risk factor for aneurysmal subarachnoid hemorrhage and acute onset of a severe headache (usually described by patients as “the worst headache of my life”) is the usual presentation of aneurysmal SAH [46]. SAH is also the only variety of stroke that is seen up to five times more commonly in women than men suggesting the role of reproductive factors in its etiology [47].

The risks of SAH are lower in women whose first pregnancy is at an older age and women who ever used HRT but not OCPs. Aneurysmal SAH occurs more commonly in the primiparae and in the third trimester of pregnancy and remains the most common cause of SAH. The reported prevalence of SAH during pregnancy is 1/10,000 patients [48].

The incidence of SAH is also highest after menopause suggesting a protective role of estrogen in the condition [49]. Increased risk of SAH is also associated with earlier age at menarche (adjusted odds ratio (AOR) 3.24 for age <13 years, 95% CI 1.25–4.03) and nulligravidity (AOR = 4.23, 95% CI 1.05–7.56). No significant association of SAH risk was found with the regularity of menstrual cycles, age at pregnancy, age at first birth, and a number of births. Aneurysmal subarachnoid hemorrhage was more common than non-aneurysmal causes.

The surgical management for the same requires emergent aneurysm clipping under the microscope. Conservative management to prevent early and late complications of subarachnoid hemorrhage is also required. Delayed surgery or coiling or conservative management only is advocated for poor patient condition, basilar artery aneurysms, and unusually large or irregular aneurysms. Postoperative course is similar in both sexes but late recurrence of subarachnoid hemorrhage occurs to a greater extent in women than men [49].

## Ischemic Strokes and Their Management

As discussed above, ischemic strokes, occurring due to any of the etiologies, present with focal neurological abnormalities. Clinical signs and radiographic findings help to diagnose and localize the site of occlusion. Use of NCCT in these cases should not be clinically withheld if clinically indicated, as the exposure of the fetus to radiation is usually low and hence a CT imaging should be done initially in all cases. Fetal radiation up to 1 mGy is acceptable [50, 51]. As gadolinium is known to cross the placenta, MRI is usually performed without contrast. Diffusion-weighted imaging is of special significance in diagnosing a stroke within the window period amenable to thrombolytic therapy.

---

## Management of Pregnancy-Related Strokes

***Antiplatelets and Anticoagulants*** Low dose aspirin and low molecular weight heparins (LMWH) have proven to be effective in reducing perinatal deaths and controlling pre-eclampsia in treating women with antiphospholipid syndrome and recurrent pregnancy loss. Meta-analysis of 14 randomized studies proved that low dose aspirin (50–150 mg/day) administered during second and third trimesters of pregnancy was safe to both mother and fetus. Data have been limited regarding safety and efficacy of other antiplatelets during pregnancy; however, Clopidogrel, a category “B” drug in pregnancy may find use in patients with high risk vascular diseases or aspirin intolerance. Similarly, therapeutic anticoagulation during pregnancy is indicated for high risk women with a history of venous thromboembolism, antiphospholipid syndrome with recurrent miscarriages, mechanical heart valves, and ongoing arterial or venous thromboembolism [39]. American Heart Association/American Stroke Association guideline for stroke prevention in 2006 also recommends administration of unfractionated heparin (UFH) or LMWH. However, caution must be exercised for the development of heparin-induced thrombocytopenia which can occur in up to 3% of patients receiving UFH [52].

***Recombinant Tissue Plasminogen Activator (rtPA)*** rtPA is a category C drug which does not cross the placenta and does not cause any teratogenicity. While it remains a relative contraindication to administer it in pregnancy, several case series have reported successful outcomes after using it in pregnant women, and in most



cases for infants when mothers did not choose elective termination of pregnancy [38]. Management of ischemic strokes in the acute period involves administration of recombinant tissue plasminogen activator (rtPA). Administered within 3–4.5 h of ischemic strokes, it decreases the risk of mortality improving 90-day post-stroke outcome with a collateral of approximately 6% risk of hemorrhage [53]. Overall, using thrombolytics in pregnancy can be said to offer a relatively safe collateral for complications, especially considering the severity of conditions for which their use is sought [54, 55].

***Endovascular Stroke Therapy*** Mechanical thrombectomy has been recently reported in two separate case reports in pregnant patients who presented with acute stroke with a high presentation NIHSS and made a good recovery after use of mechanical thrombectomy [56]. Although the use of such devices has not yet been established, mechanical thrombectomy can be tried in patients presenting with acute stroke where results with thrombolysis are likely to be poor. Radiation risk to the fetus, especially if the stroke occurs in the third trimester, can be restricted by several methods as restricting the number of angiographic exposures, using low dose fluoroscopy, pulsed fluoroscopy, tight collimation, and radiation shields [57].

Hemorrhages can occur in either subarachnoid location due to rupture of an intracranial aneurysm or secondary to uncontrolled hypertension. Management of intracranial hemorrhages must aim at targeting the cause. This includes emergent control of hypertension, diagnosis of ruptured aneurysms, or arterio-venous malformations which require surgical management [58].

---

## Pre-eclampsia and Eclampsia

Pre-eclampsia is accountable for causing as much as 60,000 mortalities per year worldwide due to eclampsia, intracranial hemorrhage, and cerebral edema accounting for nearly 75% of the fatalities. Of the reversible pregnancy-related ischemic strokes, pre-eclampsia accounts for nearly 50% of the total [59]. The strokes are mainly hemorrhagic in nature in up to 60% of the cases with uncontrolled eclampsia [60]. Eclampsia is also known to present as a posterior reversible encephalopathy syndrome (PRES). Management of these conditions should aim at control of blood pressure and parenteral magnesium sulfate. Timely termination of pregnancy is the definitive treatment of the condition and should be carried out emergently in uncontrolled cases [61].

---

## Conclusions

The myriad conditions that can complicate pregnancy can lead to varied symptoms and presentations. The onus on the physician is to connect the divergent dots against a background of a physiological extreme called pregnancy. A knowledge of the

behavior of the varied pathologies should aid in an early diagnosis of the different etiologies. Institution of the appropriate intervention techniques can help avert potential mortalities and lead to improved fetal and maternal outcomes.

## References

1. Heidemann BH, McClure JH. Changes in maternal physiology during pregnancy. *BJA CEPD Rev.* 2003;3(3):65–8.
2. Dreyfus M, Tissier I, Baldauf JJ, Ritter J. HELLP syndrome. Review and update. *J Gynécol Obstét Biol Reprod.* 1997;26(1):9–15.
3. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. *BMC Pregnancy Childbirth.* 2009;9:8.
4. Paul BS, Juneja SK, Paul G, Gupta S. Spectrum of neurological complications in HELLP syndrome. *Neurol India.* 2013;61(5):467–71.
5. Saphier CJ, Repke JT. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a review of diagnosis and management. *Semin Perinatol.* 1998;22(2):118–33.
6. Barton JR, Sibai BM. Diagnosis and management of hemolysis, elevated liver enzymes, and low platelets syndrome. *Clin Perinatol.* 2004;31(4):807–33, vii.
7. Demopoulos A, DeAngelis LM. Neurologic complications of leukemia. *Curr Opin Neurol.* 2002;15(6):691–9.
8. Chamberlain MC. Neurologic complications of leukemia. In: Schiff D, Kesari S, Wen PY, editors. *Cancer neurology in clinical practice* [Internet]. New York: Humana Press; 2008 [cited 2016 Aug 6]. p. 555–565. [http://link.springer.com/chapter/10.1007/978-1-59745-412-4\\_29](http://link.springer.com/chapter/10.1007/978-1-59745-412-4_29).
9. Rogers LR. Cerebrovascular complications in cancer patients. *Neurol Clin.* 2003;21(1):167–92.
10. Mahmoud HK, Samra MA, Fathy GM. Hematologic malignancies during pregnancy: a review. *J Adv Res.* 2016;7(4):589–96.
11. Weisz B, Meirow D, Schiff E, Lishner M. Impact and treatment of cancer during pregnancy. *Expert Rev Anticancer Ther.* 2004;4(5):889–902.
12. Penteroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N. Group O behalf of the EGW. Cancer, fertility and pregnancy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21(suppl 5):v266–73.
13. Shapira T, Pereg D, Lishner M. How I treat acute and chronic leukemia in pregnancy. *Blood Rev.* 2008;22(5):247–59.
14. Iseminger KA, Lewis MA. Ethical challenges in treating mother and fetus when cancer complicates pregnancy. *Obstet Gynecol Clin N Am.* 1998;25(2):273–85.
15. Southwick FS, Purich DL. Intracellular pathogenesis of listeriosis. *N Engl J Med.* 1996;334(12):770–6.
16. Janakiraman V. Listeriosis in pregnancy: diagnosis, treatment, and prevention. *Rev Obstet Gynecol.* 2008;1(4):179–85.
17. Abrahamian FM, Moran GJ, Talan DA. Community-acquired bacterial meningitis. *N Engl J Med.* 2006;354(13):1429–32.
18. Landrum LM, Hawkins A, Goodman JR. Pneumococcal meningitis during pregnancy: a case report and review of literature. *Infect Dis Obstet Gynecol* [Internet]. 2007 [cited 2016 Aug 11]. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1852901/>.
19. Adriani KS, Brouwer MC, van der Ende A, van de Beek D. Bacterial meningitis in pregnancy: report of six cases and review of the literature. *Clin Microbiol Infect.* 2012;18(4):345–51.
20. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39(9):1267–84.
21. Costa MLB, Souza JP, Oliveira Neto AF, Pinto E Silva JL. Cryptococcal meningitis in HIV negative pregnant women: case report and review of literature. *Rev Inst Med Trop Sao Paulo.* 2009;51(5):289–94.

22. Anzivino E, Fioriti D, Mischitelli M, Bellizzi A, Barucca V, Chiarini F, et al. Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention. *Virology*. 2009;6:40.
23. Stommel EW, Seguin R, Thadani VM, Schwartzman JD, Gilbert K, Ryan KA, et al. Cryptogenic epilepsy: an infectious etiology? *Epilepsia*. 2001;42(3):436–8.
24. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334(8):494–500.
25. Tam CS, Galanos J, Seymour JF, Pitman AG, Stark RJ, Prince HM. Reversible posterior leukoencephalopathy syndrome complicating cytotoxic chemotherapy for hematologic malignancies. *Am J Hematol*. 2004;77(1):72–6.
26. Long TR, Hein BD, Brown MJ, Rydberg CH, Wass CT. Posterior reversible encephalopathy syndrome during pregnancy: seizures in a previously healthy parturient. *J Clin Anesth*. 2007;19(2):145–8.
27. Swende TZ, Abwa T. Reversible blindness in fulminating preeclampsia. *Ann Afr Med*. 2009;8(3):189–91.
28. Postma IR, Slager S, Kremer HPH, de Groot JC, Zeeman GG. Long-term consequences of the posterior reversible encephalopathy syndrome in eclampsia and preeclampsia: a review of the obstetric and nonobstetric literature. *Obstet Gynecol Surv*. 2014;69(5):287–300.
29. Hobson EV, Craven I, Blank SC. Posterior reversible encephalopathy syndrome: a truly treatable neurologic illness. *Perit Dial Int*. 2012;32(6):590–4.
30. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. 2007;28(7):1320–7.
31. Fisher N, Saraf S, Egbert N, Homel P, Stein EG, Minkoff H. Clinical correlates of posterior reversible encephalopathy syndrome in pregnancy. *J Clin Hypertens*. 2016;18(6):522–7.
32. Otani K. Risk factors for the increased seizure frequency during pregnancy and puerperium. *Folia Psychiatr Neurol Jpn*. 1985;39(1):33–41.
33. Schmidt D, Canger R, Avanzini G, Battino D, Cusi C, Beck-Mannagetta G, et al. Change of seizure frequency in pregnant epileptic women. *J Neurol Neurosurg Psychiatry*. 1983;46(8):751–5.
34. Lu Y-T, Hsu C-W, Tsai W-C, Cheng M-Y, Shih F-Y, Fu T-Y, et al. Status epilepticus associated with pregnancy: a cohort study. *Epilepsy Behav*. 2016;59:92–7.
35. EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Neurology*. 2006;66(3):354–60.
36. Di Bonaventura C, Mari F, Vanacore N, Fattouch J, Zarabla A, Berardelli A, et al. Status epilepticus in epileptic patients: related syndromes, precipitating factors, treatment and outcome in a video-EEG population-based study. *Seizure*. 2008;17(6):535–48.
37. Elliott AB, Chakravarty EF. Immunosuppressive medications during pregnancy and lactation in women with autoimmune diseases. *Womens Health (Lond)*. 2010;6(3):431–40.
38. Tate J, Bushnell C. Pregnancy and stroke risk in women. *Womens Health (Lond)*. 2011;7(3):363–74.
39. Davie CA, O'Brien P. Stroke and pregnancy. *J Neurol Neurosurg Psychiatry*. 2008;79(3):240–5.
40. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol*. 2005;106(3):509–16.
41. Bateman BT, Olbrecht VA, Berman MF, Minehart RD, Schwamm LH, Leffert LR. Peripartum subarachnoid hemorrhage: nationwide data and institutional experience. *Anesthesiology*. 2012;116(2):324–33.
42. Bateman BT, Schumacher HC, Bushnell CD, Pile-Spellman J, Simpson LL, Sacco RL, et al. Intracerebral hemorrhage in pregnancy: frequency, risk factors, and outcome. *Neurology*. 2006;67(3):424–9.
43. Lin L-T, Tsui K-H, Cheng J-T, Cheng J-S, Huang W-C, Liou W-S, et al. Increased risk of intracranial hemorrhage in patients with pregnancy-induced hypertension: a nationwide population-based retrospective cohort study. *Medicine (Baltimore)*. 2016;95(20):e3732.
44. Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis a statement for healthcare

- professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158–92.
45. Lath R, Kumar S, Reddy R, Boola GR, Ray A, Prabhakar S, et al. Decompressive surgery for severe cerebral venous sinus thrombosis. *Neurol India*. 2010;58(3):392–7.
  46. Guida M, Altieri R, Palatucci V, Visconti F, Pascale R, Marra M, et al. Aneurysmal subarachnoid haemorrhage in pregnancy: a case series. *Transl Med UniSa*. 2012;18(2):59–63.
  47. Fox MW, Harms RW, Davis DH. Selected neurologic complications of pregnancy. *Mayo Clin Proc*. 1990;65(12):1595–618.
  48. Gaist D, Pedersen L, Cnattingius S, Sørensen HT. Parity and risk of subarachnoid hemorrhage in women: a nested case-control study based on national Swedish registries. *Stroke J Cereb Circ*. 2004;35(1):28–32.
  49. Brisman MH, Bederson JB. Surgical management of subarachnoid hemorrhage. *New Horiz*. 1997;5(4):376–86.
  50. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. *Radiographics*. 2012;32(3):897–911.
  51. Guidelines for Diagnostic Imaging During Pregnancy and Lactation—ACOG [Internet]. [cited 2017 Jul 22]. <https://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Guidelines-for-Diagnostic-Imaging-During-Pregnancy-and-Lactation>.
  52. Ginsberg JS, Kowalchuk GG, Hirsh JJ, Brill-Edwards PP, Burrows RR. Heparin therapy during pregnancy: risks to the fetus and mother. *Arch Intern Med*. 1989;149(10):2233–6.
  53. Johnson DM, Kramer DC, Cohen E, Rochon M, Rosner M, Weinberger J. Thrombolytic therapy for acute stroke in late pregnancy with intra-arterial recombinant tissue plasminogen activator. *Stroke J Cereb Circ*. 2005;36(6):e53–5.
  54. Gartman EJ. The use of thrombolytic therapy in pregnancy. *Obstet Med*. 2013;6(3):105–11.
  55. De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen PC, Luijckx GJ. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke*. 2007;38(9):2612–8.
  56. Aaron S, Shyamkumar NK, Alexander S, Babu PS, Prabhakar AT, Moses V, et al. Mechanical thrombectomy for acute ischemic stroke in pregnancy using the penumbra system. *Ann Indian Acad Neurol*. 2016;19(2):261–3.
  57. Bhogal P, Aguilar M, AlMatter M, Karck U, Bänzner H, Henkes H. Mechanical thrombectomy in pregnancy: report of 2 cases and review of the literature. *Interv Neurol*. 2017;6(1–2):49–56.
  58. Gear KE, Bushnell CD. Stroke and pregnancy: clinical presentation, evaluation, treatment and epidemiology. *Clin Obstet Gynecol*. 2013;56(2):350–9.
  59. Kittner SJ, Stern BJ, Feuser BR, Hebel R, Nagey DA, Buchholz DW, et al. Pregnancy and the risk of stroke. *N Engl J Med*. 1996;335(11):768–74.
  60. Richards A, Graham D, Bullock R. Clinicopathological study of neurological complications due to hypertensive disorders of pregnancy. *J Neurol Neurosurg Psychiatry*. 1988;51(3):416–21.
  61. Zeeman GG. Neurologic complications of pre-eclampsia. *Semin Perinatol*. 2009;33(3):166–72.

# Acute Neurological Emergencies in Drug Abusers in India

# 9

Boby Varkey Maramattom

---

## Introduction

The USA alone spent nearly 25 billion dollars on its federal drug control programme in 2015 with little to show for all its efforts [1]. In spite of this avalanche of money and effort, drug abuse has escalated all over the globe and is spiralling out of control in India. All strata of society are affected, although the economically weaker sections suffer the most due to lack of access to medical help, deaddiction and rehabilitation facilities. In India the largest category of substances that is abused is alcohol [2]. With increasing disposable incomes, the global drug trade is beginning to target India and a wide variety of drugs are now available in India. An acute neurological emergency may be the presenting feature of drug abuse and it is important to keep up to date with these presentations. Unless one has a high index of suspicion, this category of illness will not readily come to mind. As most drugs of abuse have a short half-life, it is important to consider these disorders at the initial presentation and order the appropriate investigations. Although the vast majority of such cases occur in young adult males, there is increased incidence of drug abuse in women and children. As the neurological consequences of alcohol abuse are well known and documented, this review will concentrate on other newer drugs of abuse.

---

## Clinical Features

In India, studies in teenagers have found that the most commonly abused substances are alcohol (~50%) followed by nicotine (27%), tobacco chewing (8%) and Cannabis (7%) [3]. However with increasing disposable incomes and

---

B. V. Maramattom (✉)  
Aster Medcity Hospital, Kochi, Kerala, India

**Table 9.1** Drugs of abuse or illegal prescription drugs

- 
- (a) Cannabis (marijuana, pot, grass, hash, etc.)
  - (b) Cocaine (coke, crack, etc.)
  - (c) Prescription stimulants\* (Addwize, diet pills, etc.)
  - (d) Methamphetamine (speed, ice, etc.)
  - (e) Inhalants (nitrous, glue, gas, paint thinner, etc.)
  - (f) Sedatives or sleeping pills\* (Valium, Alprax, etc.)
  - (g) Hallucinogens (LSD, acid, mushrooms, PCP, Special K, ecstasy, etc.)
  - (h) Street opioids (heroin, opium, etc.)
  - (i) Prescription opioids\* (fentanyl, oxycodone, hydrocodone, methadone, buprenorphine, etc.)
- 

\*Illegal prescription drugs

urbanisation, a larger palette of drugs is now available in India. Some of the new entrants include ‘club drugs’ or ‘designer drugs’ such as amphetamine-like substances (ATS) [4]. The use of these substances is an increasing problem in Goa and other north Indian cities. Many physicians are unfamiliar with these substances and may not recognise intoxication with such agents. The use of these substances may be rampant in ‘rave parties’ as these are often deemed ‘safer drugs’. Unlike conventional drugs, intoxication with these drugs is difficult to detect clinically or by tests. Tests to readily detect these substances are not freely available and the routine toxicology studies are often unhelpful. Moreover most of these drugs do not have an antidote.

In general, neurological consequences depend upon the class of drug abused, the particular drug used, inadvertent contaminants, route of administration and dose/frequency of administration. Moreover poly-substance abuse along with alcohol intoxication complicates presentations. Certain classic presentations should alert the neurologist to the possibility of drugs of abuse; these include strokes in the young, unusual neurological illnesses and infective endocarditis.

However, it is not always easy to attribute a particular clinical picture to a specific drug as many recreational drugs have similar presentations. Moreover drug users are known to mix drugs, employ polypharmacy and utilise different methods of intake. Additionally, drug use is often complicated by alcohol abuse. The vast majority of drug use passes off uneventfully and only a minority of users develop clinical complications.

It is important to specifically question the patient regarding various drugs of abuse or illegal prescription drugs (Table 9.1).

---

## Investigations Including Neuroimaging

It is necessary to have a high index of suspicion for drug abuse, because the window of testing is very small in these situations. Most laboratories will perform a urine toxicology screen at least for opioids and benzodiazepines. Other drugs may require more specialised labs and are not freely available in India. It is imperative to perform blood and urine toxicology screens as early as possible as some drugs have very short half-lives.

**Table 9.2** Commonly used investigations in patients with suspected drug abuse

- 
- Blood alcohol levels
  - Urine for benzodiazepines and opioids
  - Liver function tests, complete blood counts
  - Vitamin B12 and folate levels
  - Serology for HIV, hepatitis B and C, syphilis
  - Blood cultures
  - Echocardiography [TTE/TEE]
  - CT/MRI brain
  - Lumbar punctures
  - Transcranial Doppler
- 
- Routine blood tests are often necessary to rule out other organ dysfunction. Blood cultures can be helpful in cases of infective endocarditis. Serology for hepatitis B and C viruses, HIV and syphilis are helpful as many users indulge in risky injection practices and high risk sexual behaviour.
  - Neuroimaging with CT and MRI are indicated to rule out intracranial or spinal pathology. CT or MR angiography are appropriate in cerebrovascular accidents to look for vascular anomalies, although 4 vessel DSA is more useful if mycotic aneurysms or drug induced vasculitis are suspected. MRI can reveal specific patterns such as HSLE which corroborates the clinical diagnosis.
  - Echocardiography and transoesophageal echocardiography (TEE) might help to rule out infective endocarditis.
  - Transcranial Doppler (TCD) might show an increased pulsatility index in the intracranial vessels secondary to vasoconstriction [5]. TCD is also more sensitive than TEE in the detection of a patent foramen ovale and paradoxical embolism [6].
  - Lumbar puncture and CSF examination is helpful to rule out CNS infections (Table 9.2).
- 

## General Management Guidelines

### Specific Intoxicants

As alcohol abuse is well recognised and described in the literature, this review will mostly concentrate on other drugs of abuse (DOA) which have catastrophic neurological consequences.

In general, these can be subdivided into four broad groups of recreational drugs or drugs of abuse: stimulants, sedatives, hallucinogens and organic solvents [7]. Clinical consequences of drug abuse can result from acute intoxication, secondary complications or withdrawal syndromes. This review will mostly deal with the first two conditions as withdrawal syndromes usually fall under the purview of psychiatry (Table 9.3).

**Table 9.3** Common recreational drugs

Stimulants	Cocaine or crack, amphetamine, MDMA (ecstasy), methylphenidate and novel designer drugs (mephedrone, methylone, naphyrone and methylenedioxypyrovalerone)
Sedatives	Opiates (heroin) Benzodiazepines (alprazolam and diazepam) Barbiturates
Hallucinogens	Ketamine Phencyclidine (PCP, angel dust) LSD GHB
Organic solvents	Ink eraser fluid, glue adhesives, shoe polish, gasoline, spray paints or paint thinners, marker pens and lighter fluid. Toluene, hexane or benzene solvents

## Stimulants

Common stimulants include cocaine or crack, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA or ‘ecstasy’) and methylphenidate. Novel designer drugs which are substituted cathinones (e.g., mephedrone, methylone, naphyrone and methylenedioxypyrovalerone) are now available under the euphemism of ‘bath salts’ [8, 9]. These are actually the primary active alkaloid in the natural herbal stimulant khat or qat (*catha edulis*) and are amphetamine-like stimulants.

Most of these drugs act by facilitating catecholaminergic and dopaminergic neurotransmission.

## Clinical Features

Common clinical manifestations include mood elevation, increased endurance and alertness. With toxic doses, CNS stimulant effects predominate and patients develop seizures, agitation, tremors, myoclonus, psychoses or cerebrovascular accidents. Sympathomimetic excess leads to fever, hypertension and cardiac arrhythmias. Concomitant alcohol consumption greatly increases the risk of sudden death. ‘Crack cocaine’ which is often smoked is frequently associated with seizures which may progress to status epilepticus. Cocaine may also be associated with an acute hyperpyrexia and renal failure mimicking neuroleptic malignant syndrome (NMS) [10, 11]. Acute movement disorder emergencies such as acute dystonic reactions or tics are reported. Crack cocaine can cause dramatic chorea and buccolingual dyskinesias, known as ‘crack dancing’, where sufferers have self-limiting, choreoathetoid movements involving orofacial and limb musculature lasting for many days. ‘Ecstasy’ (3,4-methylene, dioxymethylamphetamine) is a widely available party drug. It is hallucinogenic at low doses and has amphetamine-like stimulant effects at higher doses. Toxicity again results in an NMS like syndrome. Cerebrovascular accidents are less common with ecstasy.

## Neuroimaging Findings

These include intracranial hemorrhage (ICH) which may be parenchymal or subarachnoid. Cocaine users have an ICH far more often than an ischemic stroke and it may be associated with an underlying vascular anomaly. The hypertensive surge



associated with cocaine is thought to be causative in these patients. Most cases of ischaemic stroke occur in the subcortical white matter, whereas mesencephalic stroke is more common when cocaine is consumed along with amphetamines. Contrast enhanced MR vessel imaging may reveal features of vessel wall vasculitis.

Midline destructive lesions may be seen in cases where cocaine is predominantly nasally inhaled. A necrotising inflammatory tissue response that closely resembles Wegener's granulomatosis (WG) with positive ANCA tests has been observed [12]. Rarely these erosive lesions may result in extensive nasal osteocartilaginous destruction and erosion of the skull base leading to a frontal lobe syndrome.

### Management

Unfortunately there are no specific antidotes available for designer drug toxicity. Nevertheless, most cases of agitation and paranoia resolve spontaneously in a few days. Supportive care in a quiet environment and prevention of self-harm may be all that is required.

Patients who develop a stroke or infective endocarditis with neurological manifestations should be managed by a multi-disciplinary team in the ICU. A dedicated stroke unit would be of great help in optimising treatment.

### Sedatives

#### Opiates

The most important opiate is heroin (diacetylmorphine) which is derived from the morphine alkaloid found in opium. It is a highly potent and addictive drug and is used in a multitude of ways, smoking, sniffing, although injectable (subcutaneous or intravenous) use is associated with the highest incidence of complications.

### Clinical Features

After an initial euphoria and other opioid effects like emesis, dry mouth and flushing, sedation sets in. Overdosage leads to coma with respiratory depression along with suppression of cough and emetic reflexes. Profound systemic hypotension or non-cardiogenic pulmonary oedema can set in. Patients can land up in the emergency room with depressed sensorium, anoxic encephalopathy, ischaemic stroke or peripheral nerve compressive palsies. Typical presentations include foot drop, bilateral sciatic nerve palsies (toilet bowl neuropathy) or other compartment syndromes [13]. Due to a high frequency of needle sharing among addicts as well as unhygienic practices, cerebrovascular accidents are common. Ischaemic stroke is associated with infective endocarditis, infective arteritis, embolism of drug contaminants such as corn starch, CNS vasculitis or paradoxical embolism. Mycotic aneurysms may be associated with intracerebral or subarachnoid haemorrhage. CNS infections such as brain abscesses, spinal cord abscess, meningitis and spinal osteomyelitis are encountered more frequently in heroin IV users than other drugs.

A peculiar clinical presentation occurring with inhalation of heroin ('chasing the dragon') is heroin spongiform leukoencephalopathy (HSLE). Patients can present with an acute ataxic quadriplegia or hemiplegia [14].

### **Barbiturates and Benzodiazepines**

The easy availability of benzodiazepines makes them a favoured drug of abuse, especially among women in India [15]. Complications are generally similar to those of heroin abuse and include coma and complications of prolonged coma.

### **Hallucinogens**

In general these drugs are uncommonly associated with neurological complications, although they alter perception.

### **Ketamine**

This is a dissociative anaesthetic with hallucinogenic properties. The use of ketamine is increasing due to its easy availability. Neurological complications after ketamine abuse are infrequent and short lived. Some patients can present with a drug induced hallucinosis, severe agitation or rhabdomyolysis [16].

### **Phencyclidine ('Angel Dust')**

This produces perceptual changes, analgesia and a hypersympathetic state. Patients can present with an acute confusional state with ataxia, dysarthria and prominent nystagmus. This can progress to seizures and coma.

### **LSD (Lysergic Acid Diethylamide)**

This is associated with cerebral infarction in a few instances, but on the whole has few neurological consequences.

### **GHB ( $\gamma$ -Hydroxybutyrate)**

Gamma-hydroxybutyrate is available as a clear liquid, white powder (soluble in water), tablet or capsule. Overdose is common, either because the concentration of the solution is unknown or because GHB is combined with alcohol or other sedatives. It can produce a rapid onset of stupor called 'G napping' [17]. At normal doses, GHB induced sleep mimics natural sleep with all its sequences. In excess, it can lead to seizures or result in prolonged anterograde amnesia. GHB can be detected by routine urine screening, but due to its short half-life, it is undetectable as early as 12 h after ingestion. Hence testing must be done as fast as possible after presentation. A few labs also offer GC-MS (mass spectroscopy) to quantify GHB levels in blood.

### **Organic Solvents**

'Glue sniffers' are often young adolescent males. In India, the common household products that contain volatile solvents and are abused include ink eraser fluid, glue adhesives, shoe polish, gasoline, spray paints or paint thinners, marker pens and

lighter fluid. Toluene, hexane or benzene solvents are often inhaled and have an immediate onset of action.

### **Clinical Features**

The effects mimic those of alcohol intoxication. As the drug effects are very short lived, repetitive use is common. The final metabolic product of toluene is hippuric acid, which is excreted by the kidneys. Long term neurological sequelae include short term memory loss, psychotic manifestations, dysarthria, ataxia along with visual, auditory and delusions or hallucinations; slurred or changed speech; staggering, stumbling, or wide-based ataxic gait. Sudden sniffing death may occur due to ventricular arrhythmias [18]. A symmetric distal predominant sensory-motor axonal neuropathy can be seen in hexane abusers. Rarely, some users can present with an acute neuropathy, mimicking GBS.

The diagnosis of glue inhalation is difficult and relies mostly on clinical examination and history obtained from the patient. Subtle clues to glue sniffing include a characteristic rash around their perioral and nasal area. Although urinary levels of hippuric acid (HA) in a freshly voided sample within 24 h of glue sniffing can be used to determine toluene exposure, this test is available only in a few laboratories [19]. Caveats to the test include the fact that HA is also naturally derived from metabolism of dietary components. Hence urinary HA levels of >1.5 to 1.6 g per gram of creatinine are necessary to indicate toluene exposure.

### **Neuroimaging**

Acute intoxication does not result in any structural imaging changes. However chronic users display a variety of imaging abnormalities. Some patients have a toxic leukoencephalopathy with subcortical cerebral and cerebellar white matter hyperintensities. Others may display diffuse cerebral or cerebellar atrophy or optic nerve atrophy on MRI [20].

### **Management**

The management of intoxication with these substances is with supportive care. The primarily role of the clinician is to assist the patient in rehabilitation and addiction treatment.

---

## **Conclusion**

Due to increasing urbanisation and disposable incomes, India is experiencing a tremendous increase in recreational substance abuse. Many of the clinical features of intoxication are non-specific. Unless one has a high index of suspicion and orders immediate and focused laboratory investigations, these disorders are likely to be missed. The increasing proliferation of designer drugs and newer agents is likely to lead to unusual clinical presentations in neurological emergency rooms.

## References

1. White House Office of National Drug Control Policy. National drug control budget: FY2016 funding highlights. Washington: Office of National Drug Control Policy; 2015.
2. Thara R, Patel V. Role of non-governmental organizations in mental health in India. *Indian J Psychiatry*. 2010;52(Suppl 1):S389–95.
3. Ray R, editor. The extent, pattern and trends of drug abuse in India: national survey. New Delhi: United Nations Office on Drugs and Crime-Regional Office for South Asia; 2004.
4. Chakraborty K, Neogi R, Basu D. Club drugs: review of the ‘rave’ with a note of concern for the Indian scenario. *Indian J Med Res*. 2011;133:594–604.
5. Herding RI, Better WE, Tate K, et al. Marijuana abusers are at increased risk of stroke: preliminary evidence from cerebrovascular perfusion data. *Ann NY Acad Sci*. 2001;939:413–5.
6. Katsanos AH, Psaltopoulou T, Sergentanis TN, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. 2016;79(4):625–35. <https://doi.org/10.1002/ana.24609>.
7. Enevoldson TP. Recreational drugs and their neurological consequences. *J Neurol Neurosurg Psychiatry*. 2004;75:9–15.
8. Weaver MF, Hopper JA, Gunderson EW. Designer drugs 2015: assessment and management. *Addict Sci Clin Pract*. 2015;10:8.
9. Karch SB. Cathinone neurotoxicity (The “3Ms”). *Curr Neuropharmacol*. 2015 Jan;13(1):21–5.
10. Merigian KS, Roberts JR. Cocaine intoxication: hyperpyrexia, rhabdomyolysis and acute renal failure. *J Toxicol Clin Toxicol*. 1987;25(1–2):135–48.
11. Singhal PC, Rubin RB, Peters A, Santiago A, Neugarten J. Rhabdomyolysis and acute renal failure associated with cocaine abuse. *J Toxicol Clin Toxicol*. 1990;28(3):321–30.
12. Stahelin L, Fialho SC, Neves FS, Junckes L, Werner de Castro GR, Pereira IA. Cocaine-induced midline destruction lesions with positive ANCA test mimicking Wegener’s granulomatosis. *Rev Bras Reumatol*. 2012;52(3):431–7.
13. Dubil EA, Dahle JM, Owens MD. Bilateral sciatic nerve palsy: a new presentation of toilet bowl neuropathy. *J Emerg Med*. 2012;43(4):622–4.
14. Kass-Hout T, Kass-Hout O, Darkhabani MZ, Mokin M, Mehta B, Radovic V. Chasing the dragon—heroin-associated spongiform leukoencephalopathy. *J Med Toxicol*. 2011;7(3):240–2.
15. Nebhinani N, Sarkar S, Gupta S, Mattoo SK, Basu D. Demographic and clinical profile of substance abusing women seeking treatment at a de-addiction center in North India. *Ind Psychiatry J*. 2013;22(1):12–6.
16. Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med*. 2000;18(4):447–51.
17. Barker JC, Karsoho H. Hazardous use of gamma hydroxybutyrate: driving under the influence. *Subst Use Misuse*. 2008;43:1507–20.
18. Avella J, Wilson JC, Lehrer M. Fatal cardiac arrhythmia after repeated exposure to 1,1-difluoroethane (DFE). *Am J Forensic Med Pathol*. 2006;27:58–60.
19. Jain R, Verma A. Laboratory approach for diagnosis of toluene-based inhalant abuse in a clinical setting. *J Pharm Bioallied Sci*. 2016;8(1):18–22.
20. Geibprasert S, Gallucci M, Krings T. Addictive illegal drugs: structural neuroimaging. *AJNR Am J Neuroradiol*. 2010;31(5):803–8.

# Neuro-Oncology Emergencies Induced by Chemotherapy

# 10

Indranil Ghosh and Sameer Bakhshi

## Introduction

The central nervous system (CNS) and peripheral nervous system (PNS) are the frequent site of toxicity of chemotherapeutic agents [1]. The toxicity could manifest itself in a myriad of ways. This toxicity can manifest in many ways, including peripheral neuropathy, encephalopathy, seizures, visual loss, etc. For many drugs, the toxicity is related to route of administration and cumulative dose, and can vary from brief, transient episodes to more severe, chronic sequelae. Many of their adverse effects are unpredictable and irreversible, and thus may lead to serious long-term sequelae [2, 3]. With increasing use of dose-intense or myeloablative chemotherapy, neurotoxicity is becoming the dose-limiting factor in many situations. Whereas systemically administered drugs chiefly cause encephalopathy and seizures, intrathecally administered drugs may cause aseptic meningitis and spinal cord toxicity. Both oncologists and neurologists should be aware of these toxicities, their clinical presentation, prevention and treatment, if any. The following sections discuss some of the well-described effects of commonly used agents. Table 10.1 highlights the various sites of drug toxicity and the common drugs associated with the same.

## Systemic Agents

### Ifosfamide

It is an alkylating agent which is converted in the liver to the active metabolite, ifosforamide mustard. Another alternative pathway, N-dechloroethylation, leads to

---

I. Ghosh  
Apollo, Kolkata, India

S. Bakhshi (✉)  
Department of Medical Oncology, Dr B.R.A. Institute Rotary Cancer Hospital,  
All India Institute of Medical Sciences, New Delhi, India

**Table 10.1** Toxicity of chemotherapeutic agents

Site of involvement	Common drugs
<i>Peripheral nervous system</i>	
Peripheral neuropathy/dorsal root ganglion	Cisplatin Oxaliplatin Vincristine Vinblastine Vindesine Bortezomib Paclitaxel Docetaxel
<i>Central nervous system effects</i>	
Delirium/encephalopathy	Cisplatin 5-fluorouracil Ifosphamide Methotrexate Nitrosoureas Etoposide Vincristine Interferons
Posterior reversible encephalopathy syndrome (PRES)	Cyclophosphamide L-asparaginase Bevacizumab Cyclosporine Ifosphamide Sorafenib
Seizures	L-asparaginase Cisplatin Cyclosporine Methotrexate Etoposide Busulphan
Visual loss	Bevacizumab Fludarabine
Cerebellar toxicity	Cytarabine Procarbazine Vincristine L-Asparaginase
Meningitis aseptic	Cytarabine Methotrexate

Modified from: Nolan CP, DeAngelis LM. Neurologic complications of chemotherapy and radiation therapy. *Continuum*. 2015;21:429–451

the generation of chloroacetaldehyde (CAA), which is structurally similar to chloral hydrate and acetaldehyde. CAA can cross the blood–brain barrier and is believed to cause CNS effects either by direct influence or by the inhibition of mitochondrial oxidative phosphorylation. The risk factors for development of ifosfamide encephalopathy are outlined in Table 10.2. However, encephalopathy can occur in the absence of the above-mentioned factors and is generally not dose-related.

**Table 10.2** Risk factors for ifosfamide neurotoxicity

- 
- Hypoalbuminaemia
  - Renal derangement
  - Prior prolonged cisplatin use
  - Concomitant opioid use
  - Diagnosis of sarcoma (vs lymphoma)
  - Concomitant aprepitant use
- 

## Clinical Features

The onset of ifosfamide encephalopathy occurs most often during or shortly after the infusion. Common symptoms are confusion, disorientation, hallucinations, psychosis, seizures, cranial nerve palsies, extrapyramidal manifestations, with progression to coma in a few cases. Although the manifestations are reversible in most patients after cessation of administration, cases with unrelenting progression and fatal outcome have been reported. The incidence is presumed to be 5–10% [4].

## Diagnosis

This is essentially clinical, although normal brain imaging and electroencephalogram (EEG) findings of metabolic encephalopathy are often useful in ruling out other diagnoses.

## Treatment

Discontinuation of ifosfamide and supportive care are the most effective treatment measures. Some observational studies have suggested that the use of methylene blue (MB) may lead to an earlier recovery [1]. MB at a dose of 50 mg intravenously every 4 hourly (1% aqueous solution given over 5 min) for treatment, and 50 mg every 6 hourly (oral or intravenous) for secondary prophylaxis has been recommended on the basis of these reports. However, there have been no randomized trials to address this issue, and hence use of MB for ifosfamide encephalopathy should be considered investigational. The same holds true for other modalities, such as intravenous thiamine and albumin. Haemodialysis can effectively remove ifosfamide metabolites from the blood and may be used in severe cases, especially in patients with renal dysfunction. Although rechallenge with ifosfamide along with MB prophylaxis has been successful in some cases, it is generally avoided.

## Prognosis

Most cases have complete neurological recovery. However, rarely, there may be progressive encephalopathy or subacute CNS degeneration and death.

## Methotrexate (MTX)

The effects of MTX in the CNS are mediated either directly or by alteration of the biochemical pathways. Decreased S-adenosylmethionine and tetrahydrobiopterin,

and increased homocysteine, sulphur-containing amino acids, and adenosine levels in the CNS are often found [5].

Neurotoxicity caused by MTX can be acute, subacute or delayed [6].

- *Acute toxicity*: Occurs within hours of administration of a high dose. It manifests as confusion, disorientation, seizures, stupor or even coma. It usually subsides within hours to days of stopping the drug.
- *Subacute toxicity*: Manifests within days to weeks of administration, with features of hemiparesis, ataxia, speech disorders, seizures, confusion and affective disturbances. The features are often 'stroke-like'. It is presumed to be caused by white matter oedema. Recovery occurs within 48–72 h and re-treatment is often possible.
- *Delayed toxicity*: Generally manifests as leucoencephalopathy, and is the most devastating complication of MTX in the CNS. Although mostly seen in children, it is also well known in long-term survivors of primary CNS lymphoma treated with radiotherapy (RT) and high-dose MTX. RT preceding MTX was the most significant predisposing factor [7]. In a study of paediatric acute lymphoblastic leukaemia (ALL) patients treated with high-dose MTX, symptomatic neurotoxicity was around 4% but subclinical neurotoxicity (detected on routine MRI) was as high as 20%. It persisted in more than half of the patients at the end of therapy [8].

### Clinical Features

Patients with delayed MTX toxicity present with confusion, somnolence or agitation, visual and speech disturbances, seizures, ataxia and dementia. Besides leucoencephalopathy, chronic toxicity may be associated with significant neuropsychological dysfunctions, such as learning disability, cognitive disturbances and decrease in intelligence.

### Diagnosis

The history of MTX use is essential. MRI of the brain in delayed MTX toxicity may reveal demyelination (Fig. 10.1a, b), multifocal white matter necrosis, astrocytosis and axonal damage. Intracerebral calcifications, cerebral atrophy and mineralizing microangiopathy have also been observed.

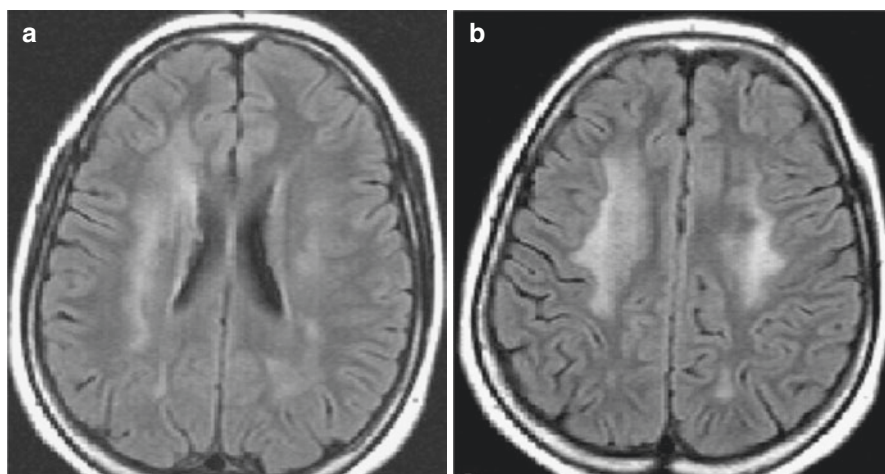
### Treatment

Delayed MTX toxicity has no effective treatment. Folinic acid has no role in prevention and treatment. Avoidance of RT before administration of high-dose MTX can prevent many cases of delayed neurotoxicity.

### Prognosis

The outcome is universally poor. Progression to quadriparesis, coma or even death is not uncommon. Sometimes, partial recovery or stabilization may occur, especially in children.





**Fig. 10.1** (a, b) MRI scan: axial FLAIR images, showing hyperintense signals in the deep white matter, suggestive of demyelination in a patient with delayed methotrexate toxicity

**Table 10.3** Risk factors for high-dose cytarabine-induced cerebellar toxicity

- 
- Higher dose ( $>36$  mg/m<sup>2</sup>)
  - Older age ( $>60$  years)
  - Renal derangement (creatinine clearance  $<60$  ml/min)
  - Severe hyperbilirubinaemia ( $>3$  mg/dl)
- 

## Cytarabine

The use of high-dose cytarabine (HIDAC) is complicated by cerebellar toxicity and the mechanism is thought to be inhibition of cytidine-dependent neurotrophic signals in the brain [6]. The incidence of cerebellar toxicity with HIDAC is ~10%. Proposed risk factors for the development of this syndrome are outlined in Table 10.3 [9].

### Clinical Features

Most commonly, the syndrome manifests as dysarthria, nystagmus and gait ataxia, sometimes progressing to confusion and somnolence. Other manifestations may include blurred vision, burning eye pain, blindness, pseudobulbar palsy and Horner syndrome. Seizures and cerebral dysfunction may occur with or without features of cerebellar toxicity.

### Diagnosis

The MRI of the brain reveals cerebellar atrophy and reversible white matter changes. The cerebrospinal fluid (CSF) is usually normal.

## **Treatment**

The neurotoxicity of cytarabine has no effective treatment. Although recovery within 2 weeks is usual, ~30% of patients may not have complete recovery. Cautious use in elderly patients and in cases of renal derangement is the key to prevention. The incidence during re-treatment in patients with prior cerebellar toxicity is >50%, and hence cytarabine should be avoided.

## **L-Asparaginase**

It induces coagulopathy by decreasing production of both coagulants (fibrinogen) and anticoagulants (antithrombin III, protein C and protein S).

## **Clinical Features**

CNS thrombosis and haemorrhage may occur in 1–2% of treated patients with the associated signs and symptoms. Cortical venous thrombosis is the most common presentation. However, encephalopathy without thrombosis may also occur, presumably due to direct neurotoxicity, and it is often associated with hyperammonaemia [10]. Excess glutaminase concentration in some preparations of L-asparaginase has also been implicated in hyperammonaemia [11].

## **Diagnosis**

Infarction or thrombosis may be detected by appropriate brain imaging (computed tomography [CT]/MRI). Diagnosis of encephalopathy is often clinical, along with a history of temporal association with L-asparaginase usage.

## **Treatment**

Thrombosis and/or infarction are managed according to existing guidelines. Treatment of encephalopathy is essentially supportive.

---

## **Intrathecal Chemotherapy**

Intrathecal (IT) administration of chemotherapeutic agents is an integral part of the current therapy for ALL and aggressive lymphomas. CNS involvement may be present at baseline in ALL, but without CNS prophylaxis with IT therapy, most patients relapse at this site. Systemic drugs have insignificant penetration into the CSF, at least in conventional doses, thus rendering the CNS a sanctuary site. To avoid the long-term sequelae of RT to the developing brain, much emphasis has been placed on IT therapy in recent times. Neurotoxicity caused by IT therapy is not rare, although serious sequelae are, fortunately, uncommon.

The commonly used agents are MTX, cytarabine and corticosteroids. If a combination has been used, it may not be possible to identify the specific agent that may be responsible for the neurotoxicity. Some of the regular syndromes associated with IT therapy are discussed below.

## Aseptic Meningitis

This is associated most commonly with the use of MTX, but may occur also with cytarabine [6].

### Clinical Features

Aseptic meningitis manifests as headache, neck stiffness, nausea, vomiting and fever within 2–4 h of administration.

### Diagnosis

In the acute phase the CSF may show pleocytosis with mild elevation of proteins, but Gram stain and cultures are negative. No other investigations are usually necessary unless neurological deficits are present.

### Treatment and Prognosis

Aseptic meningitis is self-limiting; spontaneous recovery usually occurs within 1–3 days.

## Spinal Cord Dysfunction

Although rare, it is a dreaded complication. Tetraplegia, paraplegia and cauda equina syndrome are the common manifestations.

### Clinical Features

In a review of 28 cases (mostly <18 years of age), paraplegia was observed in 23 patients (82%) and the other symptoms were tetraplegia and cauda equina syndrome [12]. In about 80% of cases, both MTX and cytarabine were used, either concurrently or sequentially. No patient received single-agent IT MTX. The median duration from IT therapy and onset of symptoms was 10 days. Bowel and urinary disturbances were most frequent, along with variable degrees of motor deficit. Sensory disturbances were infrequent.

In another report of 1395 paediatric and adolescent ALL patients who received 12–18 IT administrations each (consisting of MTX, cytarabine and methylprednisolone), 7 patients had spinal cord involvement, three had anterior horn cell involvement and another five had polyradiculoneuritis [13]. Flaccid paraplegia was the most common presentation. Only six patients recovered completely.

### Diagnosis

An MRI of the spine may show features of arachnoiditis or contrast enhancement of the cord, but most often this helps to rule out other causes, such as epidural haematoma or a tumour mass. Electrophysiological studies are required for the diagnosis of radiculoneuropathy. The CSF is usually unremarkable.

## Treatment

No specific treatment is available other than supportive care. A single case report of successful treatment of intrathecal MTX-induced progressive myelopathy with supplementation of S-adenosylmethionine, folinate, cyanocobalamin and methionine has been published [14].

## Prognosis

Functional outcome is poor, with only three and six patients, respectively, showing complete neurological recovery in the two studies cited above [12, 13]. The gravity of the initial neurological deficit and lack of recovery in the first 3 months correlate with the final outcome.

## Seizures and Encephalopathy

After IT therapy, seizures are rarely reported. In most cases, systemic agents are used concurrently, and those are the ones frequently implicated as the offenders. In the report of ALL patients cited above, the 15 patients who had received a median of three triple IT (2–17) had seizures; the median interval between the last IT and seizures was 8 days [13]. Encephalopathy is rare after IT therapy and, again, it is difficult to distinguish from that caused by systemic agents. Vincristine, however, if inadvertently used intrathecally, leads to a fatal myeloencephalopathy [15].

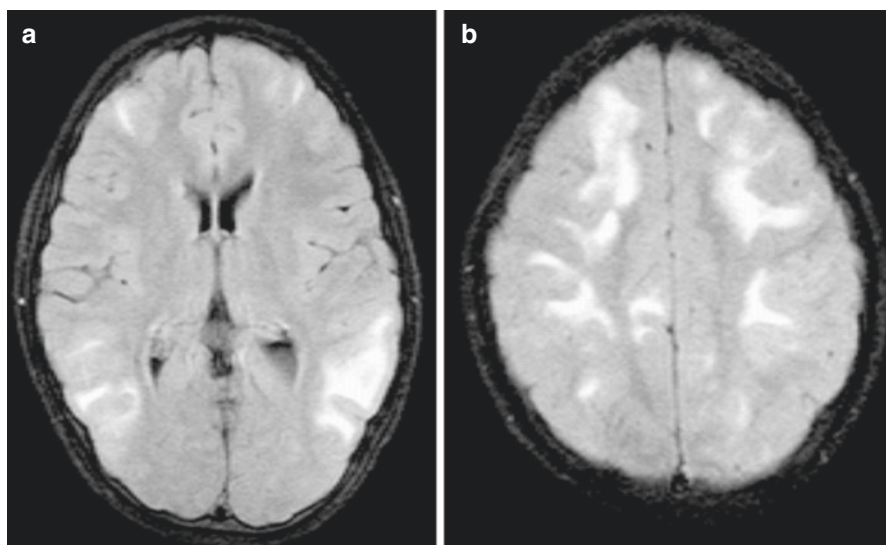
## Posterior Reversible Encephalopathy Syndrome (PRES)

It is a clinicoradiological syndrome characterized by headache, seizures, visual impairment and altered mental functioning. Because it is a syndrome with many potential inciting factors/agents, including various chemotherapy drugs, it is being discussed separately.

Although most cases are associated with hypertension (which may be corticosteroid-induced), 20–30% may be normotensive [16]. MRI of the brain (Fig. 10.2a, b) shows symmetrically distributed areas of vasogenic oedema in the posterior circulation, primarily affecting the white matter. In children with cancer, most of the PRES was commonly seen during induction of acute leukaemia, the specific reason for this timing being unclear. As ALL induction is a multi-drug protocol, identifying the offending agent may be difficult in this scenario [17]. Other drugs associated with PRES are cyclosporine, tacrolimus, cisplatin, intrathecal MTX, interferon- $\alpha$  and erythropoietin.

## Diagnosis

CT or MRI may show symmetrical areas of vasogenic oedema involving chiefly the posterior white matter. The MRI shows hyperintensities on T<sub>2</sub> and FLAIR (fluid attenuation inversion recovery) imaging, reflecting the vasogenic component (Fig. 10.1a, b).



**Fig. 10.2** MRI scan of the head in a patient with posterior reversible encephalopathy syndrome (PRES). FLAIR images (**a**, **b**) reveal hyperintensities posteriorly and anteriorly

### Treatment

This includes supportive treatment, withdrawal of potential offending agents and administration of anticonvulsants. In patients without recurrent seizures and normalization of brain imaging, it is possible to taper off anticonvulsants and reintroduce the agents, without any recurrence of symptoms.

### Prognosis

Complete clinical and radiological recovery has been reported frequently, although some reports have shown long-term sequelae in a high proportion of patients [18].

---

## References

1. Dropcho EJ. The neurologic side effects of chemotherapeutic agents. *Continuum (Minneapolis)*. 2011;17:95–112.
2. Soffiotti R, Trevisan E, Rudà R. Neurologic complications of chemotherapy and other newer and experimental approaches. *Handb Clin Neurol*. 2014;121:1199–218. <https://doi.org/10.1212/01.CON.0000464179.81957.51>.
3. Nolan CP, DeAngelis LM. Neurologic complications of chemotherapy and radiation therapy. *Continuum (Minneapolis)*. 2015;21:429–51.
4. Ajithkumar T, Parkinson C, Shamshad F, et al. Ifosfamide encephalopathy. *Clin Oncol*. 2007;19:108–14.
5. Vezmar S, Becker A, Bode U, et al. Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy*. 2003;49:92–104.
6. Verstappen CCP, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy in patients with cancer. Clinical signs and optimal management. *Drugs*. 2003;63:1549–63.

7. Correa DD, DeAngelis LM, Shi W, et al. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology*. 2004;62:548–55.
8. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32:949–59.
9. Baker WJ, Royer GL Jr, Weiss RB. Cytarabine and neurologic toxicity. *J Clin Oncol*. 1991;9:679–93.
10. Jaing TH, Lin JL, Lin YP, et al. Hyperammonemic encephalopathy after induction chemotherapy for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2009;12:955–6.
11. Derst C, Henseling J, Röhm KH. Engineering the substrate specificity of *Escherichia coli* asparaginase. II. Selective reduction of glutaminase activity by amino acid replacements at position 248. *Protein Sci*. 2000;9:2009–17.
12. Kwong YL, Yeung DYM, Chan JCW. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. *Ann Hematol*. 2009;88:193–201.
13. Dufourg MN, Landman-Parker J, Auclerc MF, et al. Age and high-dose methotrexate are associated to clinical acute encephalopathy in FRALLE 93 trial for acute lymphoblastic leukemia in children. *Leukemia*. 2007;21:238–47.
14. Ackermann R, Semmler A, Maurer GD, et al. Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites. *J Neuro-Oncol*. 2010;97:425–7.
15. Bain PG, Lantos PL, Djurovic V, et al. Intrathecal vincristine: a fatal chemotherapeutic error with devastating central nervous system effects. *J Neurol*. 1991;238:230–4.
16. Javed MA, Sail MSH, Lingaw S, et al. Etiology of posterior encephalopathy syndrome. *Pak J Med Sci*. 2005;21:149–54.
17. Gupta A, Swaroop C, Rastogi R, et al. Simultaneous occurrence of posterior reversible leukoencephalopathy syndrome in two cases of childhood acute lymphoblastic leukemia induction chemotherapy. *Pediatr Hematol Oncol*. 2008;25:351–8.
18. Morris EB, Laningham FH, Sandlund JT, et al. Posterior reversible encephalopathy syndrome in children with cancer. *Pediatr Blood Cancer*. 2007;48:152–9.

# Neurosurgical Interventions in Neurological Emergencies

# 11

Sandeep Mohindra, Rahul Gupta, and Kamal Verma

---

## Introduction

Patients harbouring neurological diseases may require urgent neurosurgical interventions. These neurological emergencies may be categorized into two broad groups, as outlined in Table 11.1. Acute ischaemic stroke (AIS) is managed by neurologists. For the select group of patients who develop malignantly raised intracranial pressure (ICP), urgent surgical intervention is required. Most of the neurological conditions requiring surgical interventions are secondary to a raised ICP, which may in turn be due to parenchymal swelling, mass effect or obstructed cerebrospinal fluid (CSF) pathways.

Decompressive craniectomies (DCs) or CSF diversion surgeries in the form of shunt insertions are, therefore, the main procedures performed when an emergent neurosurgical intervention is required.

---

## Cerebrovascular Disease

### Ischaemic Hemispheric Stroke

Malignant hemispheric infarction (Fig. 11.1a, b) is associated with mortality rates as high as 80%. This dismal outcome is related to ICP gradients, brain tissue shifts and herniation [1]. DC allows the brain to swell outwards, thereby

---

S. Mohindra (✉)

Department of Neurosurgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

R. Gupta

Department of Neurosurgery, Fortis Hospital, Noida, India

K. Verma

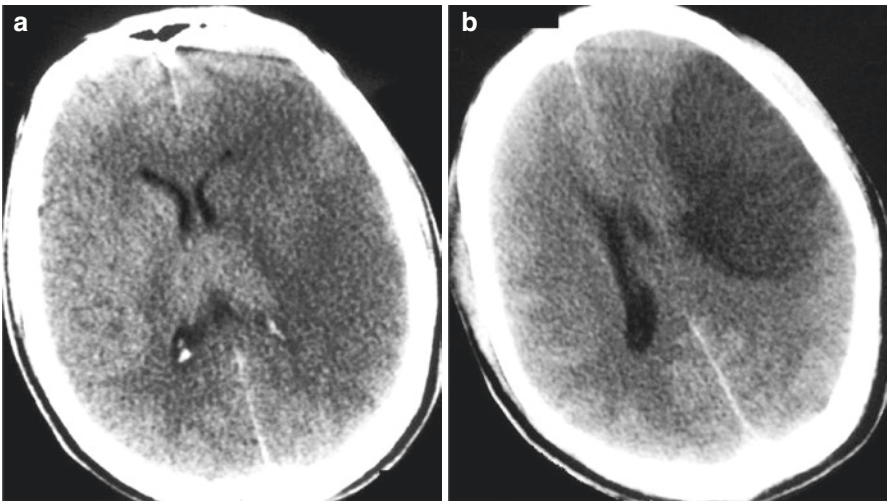
Department of Neurosurgery, Asian Institute, Faridabad, Haryana, India

**Table 11.1** Neurological emergencies—neurosurgical interventions

Type	Sub-type	Location	Neurosurgical indication	Type of intervention
Vascular	Ischaemic stroke	Supratentorial	Mass effect	Decompressive surgery
		Infratentorial	Mass effect	Decompressive surgery
			Mass effect + hydrocephalus	Decompressive surgery/VP shunt <sup>a</sup>
	ICH	Supratentorial	Mass effect	ICH evacuation
			Mass effect + hydrocephalus	ICH evacuation/temporary EVD placement/VP shunt <sup>a</sup>
		Infratentorial	Mass effect	ICH evacuation
			Mass effect + hydrocephalus	ICH evacuation/temporary EVD placement/VP shunt <sup>a</sup>
	CVT	Supratentorial	Mass effect	Decompressive surgery/ICH removal
Infective	Tubercular meningitis		Hydrocephalus	CSF diversion (VP shunt/ETV)
	Fungal meningitis		Hydrocephalus	CSF diversion (VP shunt/ETV)
			Entrapped ventricle	Selective ventricular drainage

*VP shunt* ventriculo-peritoneal shunt, *ICH* intracerebral haemorrhage, *EVD* external ventricular drain, *CVT* cerebral venous thrombosis, *CSF* cerebrospinal fluid, *ETV* endoscopic third ventriculostomy

<sup>a</sup>Options may be utilized in combinations depending upon the patient’s status



**Fig. 11.1** (a, b) CT scan head shows a large left middle cerebral artery territory infarction



equalizing pressure gradients and reducing mortality significantly [2]. It is hypothesized that DC interrupts the vicious circle of extensive brain oedema, elevation of ICP, ischaemia and further infarction. This may increase cerebral perfusion pressure and optimize retrograde perfusion of the leptomeningeal collateral vessels, thereby allowing the functionally compromised but viable brain to survive [3, 4]. The decision of when to perform a DC is guided by the fact that clinical signs precede a critically raised ICP. Studies in several cohorts of patients with large middle cerebral artery (MCA) infarctions (Fig. 11.1a, b) have shown that DC can reduce mortality to <50% [2]. Furthermore, three large concluded European randomized trials (DESTINY [5], DECIMAL [6], HAMLET [7]) have provided compelling evidence of reduced mortality and improved outcome in patients <60 years of age with IS and malignant MCA infarction, when treated within 48 h of stroke onset [1].

Meta-analysis of the published trials has shown that there is significant improvement in mortality although at the expense of survivors with disability [8].

Factors predicting the outcome of DC include advanced age, history of hypertension, side of infarction, pupillary non-reactivity, degree of midline shift and timing of surgery. Pupillary non-reactivity, involvement of the dominant hemisphere, associated co-morbidities, midline shift of >1 cm at the level of the septum pellucidum, associated posterior cerebral artery (PCA) infarct and older age result in a poor outcome. Co-existence of ipsilateral or bilateral PCA infarction is indicative of an already herniated brain and dictates a poor outcome. The clinical course of patients with severe MCA stroke may be predictable. Therefore, waiting for pupillary dilatation causes unnecessary delay, since allowing mesencephalic ischaemia to occur potentially worsens the prognosis. Further support for an earlier intervention comes from experimental studies demonstrating a better outcome in animals operated within 4 h after MCA stroke than in 12, 24 and 36 h [9]. Also, the size of the infarct was seen to reduce considerably when intervention was performed within 4 h [9].

Age has emerged as the most consistent predictor of functional outcome [1, 10]. Although the previous randomized trials have included patients up to 60 years, a recently published DESTINY 2 [11] trial included patients more than 60 years of age. In the primary outcome analysis, the proportion of patients who survived without severe disability (modified Rankin score 4–6) was higher (38%) in the hemicraniectomy group, as compared with 18% in the control group (odds ratio, 2.91; 95% confidence interval, 1.06–7.49;  $P = 0.04$ ). There was a much higher mortality among patients on best medical management (70%) versus patients undergoing hemicraniectomy (33%).

Associated co-morbidities, such as essential hypertension, diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease render these patients at higher risk for surgery. As most of the reports describing DC are of a small number of patients, and lack uniformity in patients' characteristics, it is difficult to make definite conclusions.

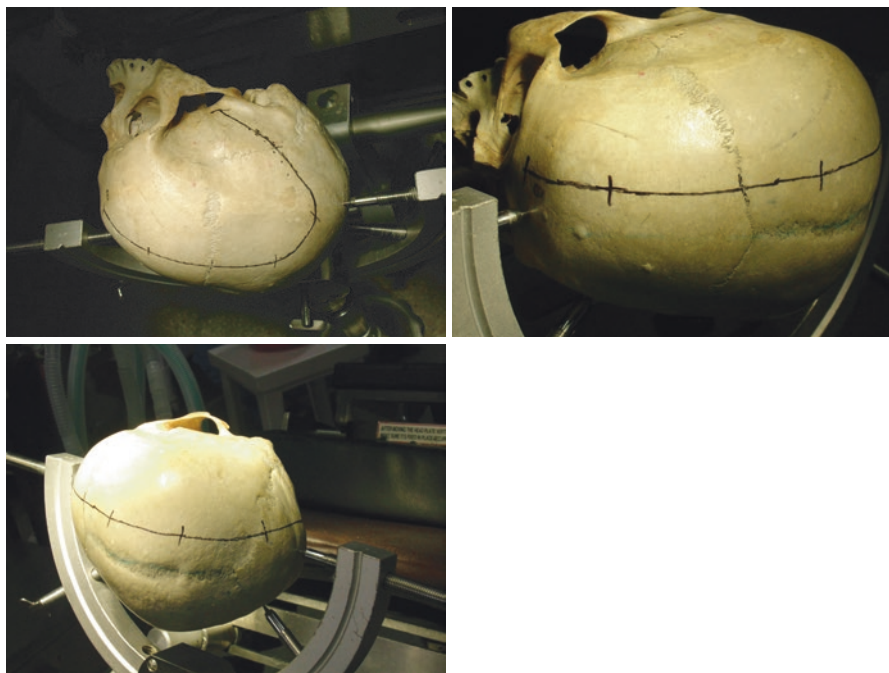
## Technique

The surgical technique of DC that our team employs is described in the literature [12–14]. We mark the skin incision (Figs. 11.2 and 11.3) starting behind the pinna, curving behind until the parietal eminence and then forward, coming parallel to midline, and reaching up to the nasion. Large bone flaps are raised (Fig. 11.4), avoiding opening of the frontal sinuses but ensuring complete removal of the temporal bone (Fig. 11.5), so as to remove all hindrances to the lateral expansion of the temporal lobe (Fig. 11.6). Durotomy is performed in a stellate fashion (Fig. 11.7), providing a large space for hemispheric expansion. Conventional duraplasty is not performed—i.e. the dura is not sutured and a dural substitute is neither sutured in nor layered on. The dura mater and exposed brain parenchyma are covered with haemostyptic material (surgical). The skin flap is closed in two layers.

Bone flaps are inserted under the abdominal fat tissues and are replaced 1–4 months post-surgery in surviving patients. Postoperatively, all patients undergo check computerized tomography (CT) scans (Fig. 11.8) and the surgical outcome is recorded on the basis of the Glasgow Outcome Score (GOS) at 6 months of follow-up.

## Complications

Massive blood loss resulting from inadvertent venous sinus injury may prove to be life-threatening. This is especially important while performing DC in elderly patients who usually have a dura mater that is adherent with their vaults.

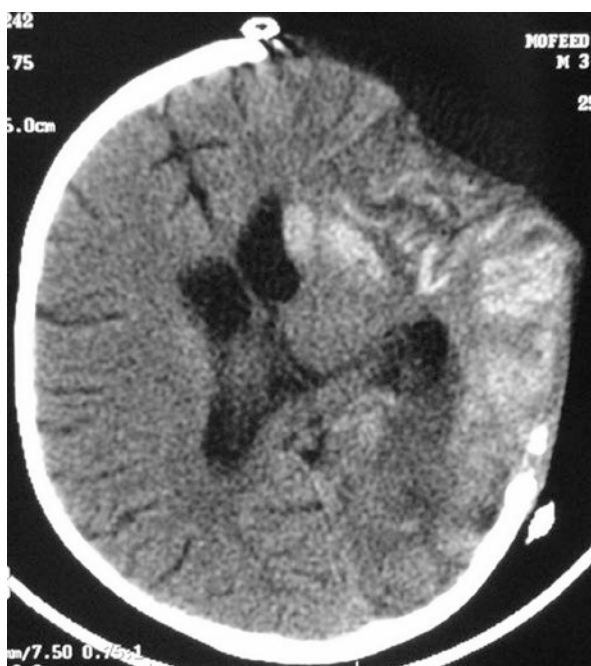


**Fig. 11.2** Bony marking on the skull fixed in 4-pin head rest detailing the amount of bone removal

**Fig. 11.3** Skin marking for decompressive craniectomy. Note the distance between the incision marking (dark continuous line) from the midline (dotted line)

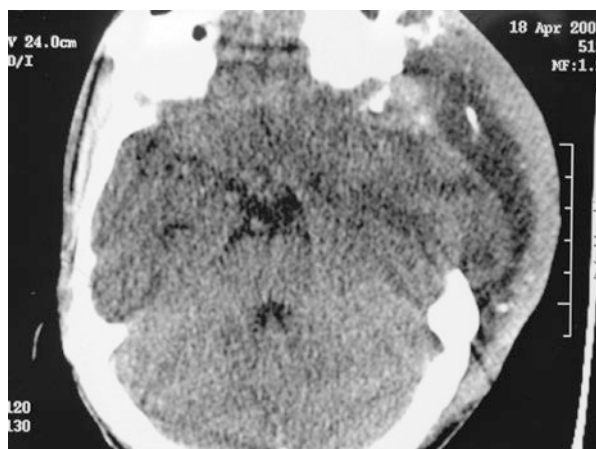


**Fig. 11.4** Axial section of a CT scan at follow-up, showing adequate hemicraniectomy, lax brain and intense gliosis

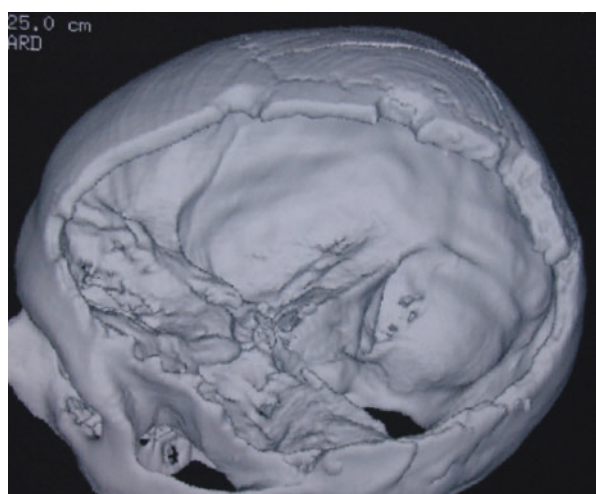


Improperly performed DCs, in which the area of bone flap removal is suboptimal, does not serve any purpose. A couple of years back, the technique and definition of DC came under severe criticism, when bony removal of as small as 30 cm<sup>2</sup> was defined as a DC [15]. Meticulous temporal bone nibbling is considered the most essential part of a DC (Figs. 11.4 and 11.6). A rapid closure technique saves time and blood loss, which is another important aspect of surgery on a rapidly deteriorating patient. Cranioplasty after a rapid closure technique should also be fast and safe [12].

**Fig. 11.5** Axial section at the level of the temporal bone, showing liberal temporal craniectomy and extensive bone removal, so as to provide free space to the temporal lobe for expansion



**Fig. 11.6** Two-dimensional reconstructed CT image showing the amount of hemicranium to be removed, so as to justify the surgery as 'decompressive craniectomy'



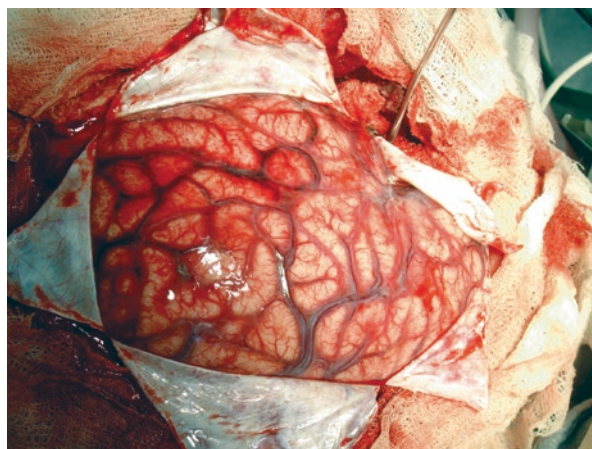
## Summary

DC seems to be an effective therapeutic intervention for malignant MCA infarction. Younger patients (<60 years of age) with no co-morbidities and involvement of the non-dominant cerebral hemispheres and with no anisocoria have a better functional outcome when a DC is performed within 12 h of initiation of symptoms. The timing of DC remains a critical question.

## Cerebral Venous Thrombosis (CVT)

CVT results from thrombosis in one or more of the dural sinuses and/or draining veins of the brain, causing venous hypertension and raised ICP. This slows the circulation leading to propagation of the thrombus, resulting in severe brain

**Fig. 11.7** Liberal durotomy so as to provide enough space for hemispheric expansion



**Fig. 11.8** Axial section of a CT scan performed after decompressive surgery, showing removal of a large bone flap and a considerably reduced size of infarct



swelling, infarction, intracerebral haemorrhage (ICH), mass effect, midline shift and herniation [16]. The annual incidence of CVT worldwide is 1.5–3 per million population. It is commoner in women, especially in the age group of 20–35 years, due to pregnancy, the puerperium and oral contraceptive usage. In a large series, the mean age was 38 years, although all ages can be affected [17]. Predisposing factors for CVT include dehydration, prolonged illness, fasting, diarrhoea, hypercoagulable states, pregnancy, the puerperium, oral contraceptive usage, infections and a postoperative state. The clinical manifestations

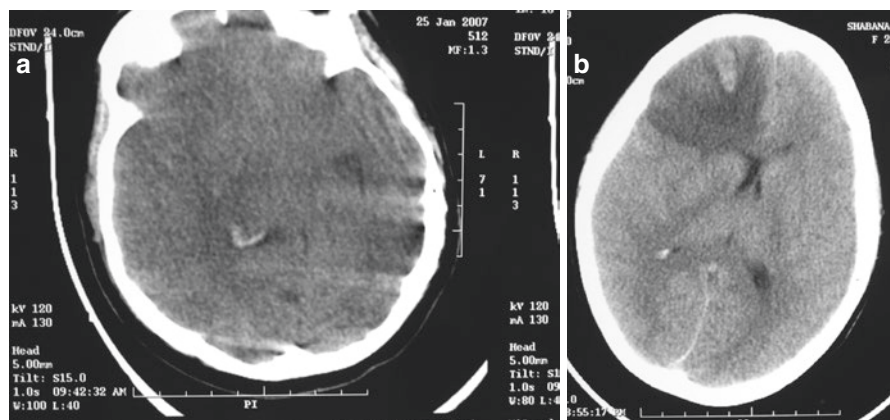


include headache (in 70–90% of cases), nausea, vomiting, altered mentation, seizures and focal neurological deficits. Symptoms pertaining to a raised ICP may ensue in due course of time.

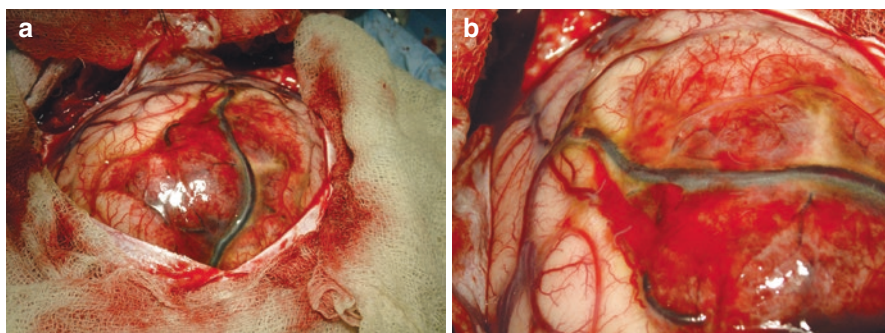
As medical management involves anticoagulation, the timing of any surgical intervention remains crucial and is an important prognostic factor for the successful outcome of such patients. Rather than the time interval from onset, it is the patient's clinical state correlated with the radiological findings which determines the timing for surgical intervention. The option of surgery may be decided whenever the patient develops an altered sensorium. The onset of coma in such patients heralds a grave prognosis, as the DC fails to break the ongoing vicious circle of brain damage [18]. DC is warranted when there is deteriorating consciousness with CT signs of massive brain swelling, venous infarction, congestion, bleeding with mass effect, midline shift and obliteration of the basal cisterns (Fig. 11.9a, b) with imminent signs of herniation. An early decision for surgical intervention at the outset of a confusional mental state of the patient may help to obtain a better outcome [19].

Surgery in the form of DC (as already described in the section on “[Ischaemic Hemispheric Stroke](#)”) is described as a relevant option for rapidly deteriorating patients, signalling the failure of medical management. Surgical decompression is defined in terms of an ‘external decompression’ (Fig. 11.10a, b) or fronto-temporo-parietal craniectomy with a wide dural opening to allow adequate brain relaxation or ‘internal decompression’ if resection of infarcted cerebral tissue and total clot removal is performed. Various studies have shown a favourable outcome (GOS 4 and 5) after an early DC [13, 18–25].

Liberal temporal craniectomy remains an essential part of the surgical procedure [13]. The bone flap may be preserved in a scalp or abdominal wall subcutaneous plane. These bone flaps may be replaced after 3 months of a DC. As the indication



**Fig. 11.9** (a) Axial section of a CT scan showing completely obliterated basal cisterns, indicating massive brain swelling. (b) Axial section of a CT scan, showing CVT involving the anterior one-third of the superior sagittal sinus



**Fig. 11.10** (a, b) Intra-operative picture showing a large craniotomy flap raised and liberal dural opening. Note thrombosis of the great vein of Trolard and peri-venous subpial bleed

for surgery is massive brain swelling, it seems logical to perform a craniectomy rather than a craniotomy.

As anticoagulation is an important part of management, even in patients with a considerable haemorrhagic component, full-dose anticoagulation may be initiated early after surgery [19]. Heparin may be started 12 h postoperatively at half dosage (9 IU/kg/h, continuous i.v.) and switched over to full dosage (18 IU/kg/h) after 24 h of surgery [18]. The dosage is targeted to attain a PTT (prothrombin time) of 2–2.5-fold without any increased risk of bleeding [18]. If a raised ICP persists in spite of extensive surgical decompression, other methods to lower the ICP should be tried [21, 22]. At follow-up, patients may have persistent papilloedema and a raised ICP, in spite of unremarkable CT scan findings. These symptoms mimic idiopathic intracranial hypertension and the patients may require surgical CSF diversion procedures to salvage vision [18].

### Summary

A favourable outcome in a select group of patients with the most severe course of CVT can be achieved by early DC. Deteriorating consciousness, along with radiological evidence of massive brain oedema, subcortical haematoma, mass effect, midline shift and obliterated basal cisterns call for an early DC, rather than letting these patients enter a state of deep coma before deciding on DC. Anticoagulant drugs are safe and essential during the peri-operative period. Surgery at an early stage of the disease may be beneficial and the choice of ‘internal’ and ‘external’ decompression may be decided upon according to individual cases. In future, techniques for decompressive surgery combined with thrombectomy deserve to be evaluated.

### Ischaemic Cerebellar Stroke

Sub-occipital DC is a life-saving intervention for patients with malignant cerebellar infarction. This surgical procedure includes placement of external ventricular drains

and resection of necrotic tissue. Associated brain stem infarction in this subgroup of IS patients determines a poor outcome and poor quality of life [26].

Data on long-term outcome are lacking [27]. Surgical management of a space-occupying cerebellar infarction remains controversial [27]. The published literature comparing ventriculostomy/extraventricular drainage or sub-occipital DC in association with each other failed to prove the superiority of any of the procedures or provide differences in survival. Age and premorbid modified Rankin scale (mRS) were the only significant independent predictors of outcome. Jüttler et al. [27] have justified the need for randomized trials to prove the benefit of such interventions, although ethical concerns for such trials have also been voiced.

## **Intracerebral haemorrhage [ICH] (see also Chap. 12)**

Spontaneous ICH is defined as haemorrhage in the brain parenchyma in the absence of immediate trauma; it can be primary or secondary. Primary ICH occurs in the absence of a structural disease process whereas secondary ICH is associated with congenital or acquired lesions, such as aneurysms, arteriovenous malformations, cavernous angiomas, tumours and vasculitis.

### **Surgery in Supratentorial Spontaneous ICH**

Kase and associates reported a good outcome in patients with a haematoma volume of  $<20\text{ cm}^3$  [28]. Seventy percent survived after surgical removal of haematomas that were  $20\text{--}60\text{ cm}^3$  in volume. It is noteworthy that no patient with a haematoma volume of  $>60\text{ cm}^3$  survived [28]. Apart from size, other factors, such as location of the ICH, ICP, degree of midline shift, amount of brain atrophy, time elapsed between ictus and resuscitative measures, and delay in surgical evacuation affected the morbidity and mortality in these patients.

The physiological effect of ICH on the brain is multi-factorial. Patients are susceptible to neurological deterioration within the first 24 h after haemorrhage, particularly the first 4–6 h [29, 30]. Several experimental models have been prepared to measure the critical size of the haematoma that needs surgical evacuation.

Although the larger the haematoma, the worse the prognosis, the volume of the haematoma alone cannot decide between the surgical and medical management of such lesions. In a retrospective study conducted by Volpin and associates, surgery decreased the mortality rate of comatose patients with a haematoma volume between  $26$  and  $85\text{ cm}^3$  [31]. However, the probability of severe neurological deficit at follow-up was high. All patients with a haematoma volume of  $>85\text{ cm}^3$  died, irrespective of the treatment, and all patients with a haematoma volume of  $<26\text{ cm}^3$  survived without surgery [31]. The data from both STICH [32] and the other smaller trials suggest that surgery does not appear to be helpful in treating most supratentorial ICH. However, in the STICH trial, 26% of patients in the medical arm underwent surgical intervention because of deterioration. A recent meta-analysis of ten randomized controlled trials suggests that surgery reduces the odds of being dead or dependent, and may benefit patients with altered consciousness and worsening sensorium [33]. Having



said this, surgery, particularly craniotomy, may be helpful in treating those lobar clots within 1 cm of the surface that present in patients with milder deficits (GCS score > 9), because both craniotomy and surface location were associated with a 29% relative benefit in functional outcome when compared with medical management. The STITCH 2 (Early Surgery Versus Initial Conservative Treatment In Patients With Spontaneous Supratentorial Lobar Intracerebral Haematomas) was published recently [34]. A total of 601 patients with bleeds close to the surface were randomized to either early surgery or initial conservative treatment; 59% patients in the early surgery group had an unfavourable outcome versus 62% patients in the initial conservative treatment group (absolute difference 3.7% [95% CI -4.3 to 11.6], odds ratio 0.86 [0.62 to 1.20];  $p = 0.367$ ). Although the trial could not show a statistically significant difference among groups on outcomes, it did suggest a small benefit on survival and dependence at 6 months among the surgically operated group. Again, the trial had a crossover design as the original STITCH trial.

A randomized, prospective study comparing endoscopic removal of supratentorial ICH with medical management found surgery to be beneficial for haematomas of all volumes. The overall lower surgical mortality rate of 30% has encouraged endoscopic removal of ICH at many centres [33, 35].

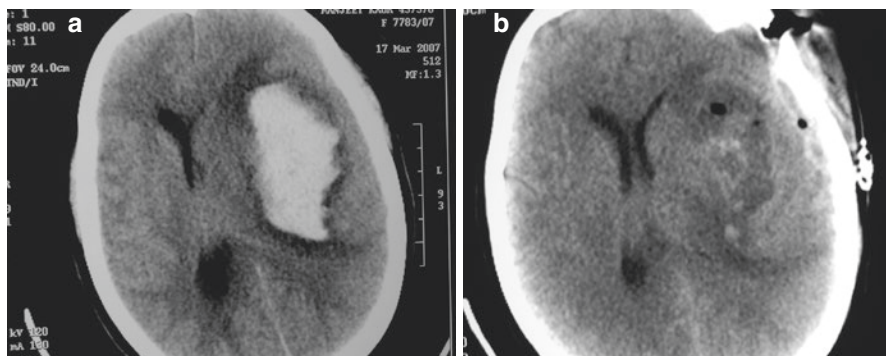
Age plays an important role in deciding on a surgical option to manage these patients. An age of >60 years implies poor prognosis regardless of treatment. Surgical evacuation of the haematoma is best avoided in these patients. In the study by Auer et al., patients younger than 60 years had a 25% mortality compared with 65% in the older group [35]. Early haematoma growth is also a critical determinant of outcome in ICH. This may suggest the importance of early haematoma evacuation to reduce peri-haematoma ischaemia, toxic effects of blood products and potential progression of the haematoma [30, 36].

The importance of early surgery cannot be over-emphasized and several studies have indicated better clinical outcomes with surgery as it improves the cerebral blood flow, brain oedema, ischaemia and even histological changes [30, 31]. The concept of early surgery (especially ultra-early surgery, within 6 h) can only be feasible if primary physicians, paramedics and the public are aware of this entity in the form of 'brain attack', and the patient is able to reach the hospital within 3 h of ictus. A randomized, controlled, prospective trial by Zuccarello et al. did not find any differences in outcome between surgery and medical management when patients arrived at the hospital after 3 h and were operated on beyond the 'safe' period of <6 h [37].

## **Surgical Techniques**

### **Craniotomy/Craniectomy and Evacuation**

A meticulous technique by an experienced surgeon can remove the ICH near totally without much injury to the normal brain and provide a good outcome. However, total evacuation is not the prime goal of this kind of surgery. An adequate removal to decrease the mass effect, normalize the ICP and prevent a recurrence is sufficient (Fig. 11.11a, b).



**Fig. 11.11** (a). Axial section of plain CT scan showing left-sided spontaneous putaminal bleed. (b) Postoperative CT scan showing adequately evacuated putaminal haematoma, after performing left pterional craniotomy and mid-frontal corticectomy

### Burr Hole and Aspiration

This is a simple method that can be performed under local anaesthesia. But as the blood clot may have an unpredictable consistency, removal of sufficient blood is uncommon. Also, there is a propensity for re-bleeding due to a blind approach to the lesion. In a study of 175 patients treated with this method, 7.4% had postoperative bleeding, even though 75% had >50% clot removal [38].

### Stereotactic Aspiration

Stereotactic aspiration with the help of fibrinolytics and mechanically assisted devices has improved results. Although no randomized, prospective controlled study has compared this method with open surgery or conservative treatment, existing studies show a favourable outcome in deep-seated lesions [39].

### Neuroendoscope

A promising tool to evacuate an ICH, the neuroendoscope is being used extensively these days by surgeons. It has the advantage of a smaller port of entry (a little bigger than that for stereotactic clot evacuation) to minimize damage to the brain. Also, it has the facility of coagulating the bleeding vessel to reduce the chance of recurrence. A proper randomized, prospective controlled trial comparing it with other surgical methods and also with conservative treatment is awaited to establish its role in the management of ICH.

### Fibrinolytic Therapy

This method utilizes tPA (tissue plasminogen activator) and urokinase, and has been used in various controlled studies. Since fibrinolysis may lead to re-bleeding, it is performed  $\geq 6$  h after the ictus so that it does not dissolve the protective clot [39]. In pilot human trials, Lippitz et al. [40], Schaller et al. [41] and Vespa et al. [42] reported that daily administration of tPA into the haematoma cavity beginning 12–24 h after stereotactic placement of a catheter resulted in an average reduction of 85% in the

haematoma volume by 2–4 days after onset. Based on these results, a multicentre, randomized, controlled and stratified study comparing administration of tPA into the clot cavity versus conventional medical treatment has been funded by the National Institutes of Health, USA. This study (Minimally Invasive Stereotactic Surgery + rtPA for ICH Evacuation [MISTIE]) will test the following hypotheses: (1) early use of minimally invasive surgery plus tPA for 3 days is safe for the treatment of ICH and (2) early use of minimally invasive surgery plus tPA for 3 days produces reduction in the clot size compared with that in medically treated patients. The MISTIE 3 trial was a prospective randomised open-label, clinical trial of minimally invasive surgery plus rtPA in the treatment of large ICH (>30 mL) among 506 patients [43]. Subjects were randomly assigned to receive a surgical procedure of minimally invasive image-guided hematoma aspiration plus 1 mg of rtPA instillation every 8 h through a hematoma catheter, until clot volume <10 mL or 9 doses, plus best critical care management, vs best critical care management alone. Primary outcome parameter was the improvement of functional outcome by a on the modified Rankin scale (mRS) score 0–3 compared to medically treated subjects assessed at 365 days adjusted for group differences in prespecified baseline covariates and safety measures including rate of mortality, re-bleeding and infection. The secondary outcomes measure is ICH reduction related to better functional outcome in comparison with medical management group. 45% of patients among the MISTIE group and 41% patients in the medical care group achieved an mRS score of 0–3 at 365 days (adjusted risk difference 4% [95% CI –4 to 12];  $p=0.33$ ) using modified ITT analysis. The trial suggested safety of the intervention but no benefit on functional outcome.

The second trial, Clot Lysis Evaluating Accelerated Resolution (CLEAR) uses intraventricular thrombolysis in the setting of IVH. The CLEAR IVH phase II trial assigned patients to treatment with 0.3, 1.0 or 3.0 mg of rtPA, every 8 or 12 h, vs placebo, in a prespecified manner. The reported mortality was 18% with rtPA vs 23% in the placebo group; ventriculitis rate of 8% with rtPA vs 9% in the placebo group and symptomatic bleeding of 23% with rtPA vs 5% in the placebo group. The study found that low-dose rtPA with a 1.0-mg dose every 8 h has an acceptable safety [44].

This observation leads to CLEAR III trial in which 500 patients within 12–72 h of onset of an IVH underwent insertion of a brain catheter and were randomly assigned to receive saline or tPA (1 mg) every 8 h for up to 12 doses or until the ventricles were cleared of blood [45]. Primary end point mRS at 180 days was 48% in Alteplase group vs 45% in saline group. Alteplase group had 11% overall mortality reduction, but a higher proportion of patients with mRS 5. The likelihood of a better outcome was improved with amount of blood removed, with best results in patients whom 90% clot was removed (<https://clinicaltrials.gov/ct2/show/NCT00784134?term=CLEAR+III&rank=1>). CLEAR IV trial is planned for larger clots and currently awaiting funding.

A meta-analysis was done by Gaberel et al. on four randomized and eight observational studies which included 316 patients of whom 167 underwent IVF. There was a mortality risk reduction from 46.7% in the EVD alone group to 22.7% in the EVD + IVF group, OR of 0.32 (95% CI, 0.19–0.52) with good functional outcome at  $\geq 3$  months (54% in lytic group versus 34% in the EVD-only cohort) [46].

The INVEST trial is phase II randomized controlled trial of Minimally Invasive Endoscopic Surgical (MIES) with APOLLO vs Medical Management in supratentorial ICH. The primary outcome of this study is mRS at 180 days. This study will recruit 222 patients of moderate to large (20–80 cc) supratentorial ICH presenting within 24 h of onset and investigate safety and efficacy of MIE in ICH. The trial is likely to complete Jan 2019 (<https://clinicaltrials.gov/ct2/show/NCT02654015>).

ENRICH has started enrolling patients in December 2016 which is a multicenter, randomized, adaptive clinical trial comparing standard medical management to early (<24 h) surgical hematoma evacuation using minimally invasive parafascicular surgery (MIPS) in the treatment of acute spontaneous supratentorial intracerebral haemorrhage (<https://clinicaltrials.gov/ct2/show/nct02880878?term=enrich&rank=1>).

### **Hydrocephalus After ICH, Intraventricular haemorrhage (IVH)**

Sub-analysis of data obtained through an international surgical trial in ICH showed a favourable outcome when IVH was absent (31.4% vs. 15.1%) [47]. The presence of hydrocephalus lowered the likelihood of a favourable outcome to 11.5% in patients with IVH, whereas early surgical intervention had a more favourable outcome (17.8%) compared with initial conservative management (12.4%). It was concluded that the presence of IVH and hydrocephalus are independent predictors of poor outcome in spontaneous ICH [47].

### **Surgery in Cerebellar/Brain Stem Haemorrhage**

Spontaneous cerebellar haematomas may require emergent neurosurgical intervention, in the form of ventricular drainage of CSF, temporary CSF diversion (external ventricular drainage) or haematoma evacuation. Even when no specific guidelines are available, the grading of ventricular effacement by cerebellar haematoma may provide a simplified answer in selecting surgical candidates. Appearance of the fourth ventricle adjacent to the haematoma, as evident on CT scans, is divided into three grades (normal, compressed or completely effaced). The degree of fourth ventricular compression is correlated with the size and volume of the haematoma and presenting Glasgow coma scale (GCS) score. The haematoma is surgically evacuated in all patients with Grade III compression, and for patients with Grade II compression when the GCS score deteriorates in the absence of untreated hydrocephalus. Patients with Grade I or II compression are initially treated with only ventricular drainage in the presence of hydrocephalus and clinical deterioration [48].

Rarely are spontaneous pontine haematomas large enough to warrant evacuation; patients harbouring large pontine haematomas are neurologically unfit for such a demanding surgical intervention [49].

---

## **CNS Infections**

### **Acute Hydrocephalus in Meningitis**

#### **Tubercular Meningitis (TBM).**

Hydrocephalus is one of the commonest complications of TBM, occurring in up to 85% of children [50]. Hydrocephalus may occur because of subarachnoid block

(communicating type) or because of mechanical blockage of the CSF pathways caused by tuberculomas or scarring of ependymal walls (obstructive type).

**Fig. 11.12** Axial section of CT scan showing tubercular hydrocephalus. Note the clubbing of the frontal horns and peri-ventricular lucency



**Fig. 11.13** Correctly placed shunt in a patient of tubercular hydrocephalus. Decompressed ventricular system, with open cisternal space indicates a functioning shunt



Obstructive hydrocephalus in children with TBM may present as a neurological emergency requiring urgent CSF drainage/diversion (Fig. 11.12).

Historically, repeated ventricular taps through burr holes have been used [51]. The present-day shunt systems are the best possible treatment options for hydrocephalus (Fig. 11.13).

### Indications for Surgery

Good grade (Grades I and II) patients may be offered CSF diversion surgery at the earliest [52]. Although a non-surgical approach with antitubercular treatment (ATT) and steroids is always tried for patients with communicating hydrocephalus, this theoretically harbours the risk that some patients undergoing medical therapy might deteriorate rapidly and have a poor outcome if shunt surgery is delayed [50]. Not all patients who undergo shunt surgery for hydrocephalus show a significant improvement in their sensorium or symptoms. Altered sensorium and other symptoms in these patients may not always be completely attributable to the hydrocephalus.

Patients with TBM in the poorer grades usually show infarcts of the basal ganglia, thalamus and brain stem. In these patients, it is difficult to localize the cause of the alteration of sensorium [50]. It seems prudent to offer shunt surgery in all such patients.

### CSF Diversion Surgery

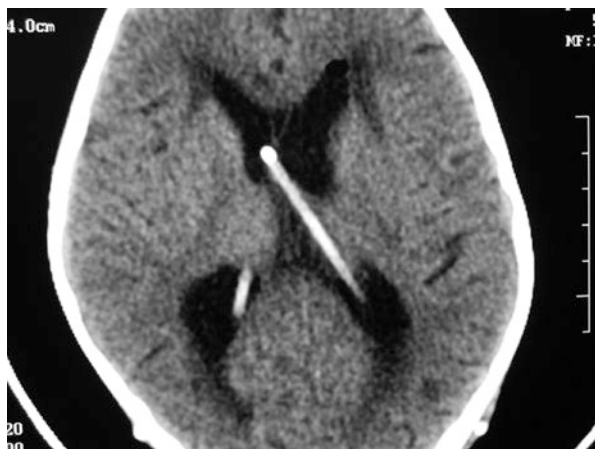
The fear of disseminating the tuberculosis disease through ventriculo-atrial shunt systems threw these systems into disrepute. Presently, the ventriculo-peritoneal (VP) shunt remains the shunt procedure of choice for patients with TBM and hydrocephalus (Figs. 11.12 and 11.13). The technique for shunt surgery does not differ from that used for hydrocephalus from any other cause.

Although endoscopic third ventriculostomy (ETV) has been described as a treatment option for tubercular hydrocephalus, its applicability seems unjustified in acute cases due to the thickened floor of the third ventricle and distorted anatomy [53]. ETV is more successful in chronic and burnt-out cases [53]. In this situation it might be prudent to abandon the procedure than risk injury to the basilar artery and its branches. We have attempted ETV in patients with TBM early in the course of the disease and found that the floor of the third ventricle, besides being thick, is coated with small tubercles and granulation tissue that bleed when touched even with a blunt probe. As bleeding of even minor intensity can obscure the field during endoscopic procedures, our group believes that ETV might be better avoided for acute hydrocephalus in patients with TBM and be reserved for those who have been treated with ATT for at least 4 weeks [54].

The utility and efficacy of ETV has been evaluated using cine MRI (cine phase-contrast MRI) in cases of tubercular hydrocephalus [54]. The measured rate of CSF flow across the ETV stoma suggests better outcomes for patients already on ATT for a longer period and in a chronic stage, thereby indicating the effectiveness of ETV for chronic cases. For acute hydrocephalus of the obstructive type, a VP shunt is indicated.



**Fig. 11.14** Multiple shunt insertions remain a hallmark of tubercular hydrocephalus



**Fig. 11.15** Clinical picture of the abdomen, showing multiple shunt site incisions, due to repeated shunt insertions



**Fig. 11.16** Clinical picture showing shunt tube erosion through the parietal wall, leaving behind a punched-out ulcer



### Complications of Surgery

The poor general condition of tubercular patients makes them more susceptible to shunt infections (Figs. 11.14, 11.15 and 11.16) and skin erosions (Fig. 11.16). Higher CSF protein and cellular content predispose these patients to shunt blocks resulting in revisions [52, 55].

### Fungal Meningitis (Aspergillosis, Cryptococcosis)

During therapy, patients with fungal meningitis may suddenly develop decreasing vision, headache, vomiting or symptoms suggestive of isolated ventricular entrapment. These patients may require CSF diversion surgery on an emergent basis. A VP shunt may be required during any time while on antifungal therapy. Acute, single ventricular entrapment requires selective ventricular drainage or a selective VP shunt. Isolated lateral ventricular entrapment is the commonest ventricular entrapment encountered in the management of meningo-encephalitis. Fourth ventricular entrapment may also occur and is life-threatening because of the restricted space and intolerability of the brain stem to raised intra-fourth-ventricular pressure. Sudden respiratory collapse may occur and calls for urgent transcerebellar fourth ventricular CSF drainage or fourth VP shunt placement.

### Summary

The grade at presentation is recognized as the best and most consistent predictor of outcome following shunt surgery in patients with TBM. Age, duration of altered sensorium, CSF cell analysis, CSF protein level, shunt revisions or bilateral shunts do not have any significant effect on the long-term outcome [50]. The presence of infarcts in the basal ganglia and internal capsule indicates a poor outcome after shunting. It is uncertain if shunt surgery can be avoided in some patients with mild-to-moderate hydrocephalus and whether it is preferable to offer them early surgery rather than wait to observe effects of medical treatment.

### References

1. Merenda A, DeGeorgia M. Craniectomy for acute ischemic stroke: how to apply the data to the bedside. *Curr Opin Neurol*. 2010;23:53–8.
2. Unterberg A, Juettler E. The role of surgery in ischemic stroke: decompressive surgery. *Curr Opin Crit Care*. 2007;13:175–9.
3. Doerfler A, Forsting M, Reith W, et al. Decompressive craniectomy in a rat model of ‘malignant’ cerebral hemispherical stroke: experimental support for an aggressive therapeutic approach. *J Neurosurg*. 1996;85:853–9.
4. Forsting M, Reith W, Schäbitz WR, et al. Decompressive craniectomy for cerebral infarction: an experimental study in rats. *Stroke*. 1995;26:259–64.
5. Hennerici M, Jüttler E, Schmiedek P, Schwab S, Unterberg A, Woitzik J, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized, controlled trial. *Stroke*. 2007;38:2518–25.



6. Guichard JP, Kurtz A, Mateo J, Orabi M, Vahedi K, Vicaut E, et al. Sequential-design, multi-center, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial). *Stroke*. 2007;38:2506–17.
7. Algra A, Amelink GJ, Hofmeijer J, Kappelle LJ, van der Worp HB, van Gijn J, HAMLET Investigators. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol*. 2009;8:326–33.
8. Alexander P, Heels-Ansdell D, Siemieniuk R, et al. Hemicraniectomy versus medical treatment with large MCA infarct: a review and meta-analysis. *BMJ Open*. 2016;6:e014390.
9. Schwab S, Steiner T, Aschoff A, et al. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–93.
10. Rabinstein AA, Mueller-Kronast N, Maramattom BV, et al. Factors predicting prognosis after decompressive hemicraniectomy for hemispheric infarction. *Neurology*. 2006;67:891–3.
11. Amiri H, Bösel J, Jüttler E, Sakowitz OW, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med*. 2014;370:1091–100.
12. Güresir E, Vatter H, Schuss P, et al. Rapid closure technique in decompressive craniectomy. *J Neurosurg*. 2011;114(4):954–60.
13. Mukherjee KK, Mohindra S, Gupta SK, et al. True hemicranial decompression for severe pediatric cranial trauma: a short series of 4 cases and literature review. *Surg Neurol*. 2006;66:305–10.
14. Ucar T, Akyuz M, Kazan S, et al. Role of decompressive surgery in the management of severe head injuries: prognostic factors and patient selection. *J Neurotrauma*. 2005;22:1311–8.
15. Compagnone C, Murray GD, Teasdale GM, et al. The management of patients with intra-dural post-traumatic mass lesions: a multicenter survey of current approaches to surgical management in 729 patients coordinated by the European Brain Injury Consortium. *Neurosurgery*. 2005;57:1183–92.
16. Stefani R, Latronico N, Cornali C, et al. Emergent decompressive craniectomy in patients with fixed dilated pupils due to cerebral venous and dural sinus thrombosis: report of three cases. *Neurosurgery*. 1999;45:626–30.
17. Allrogen H, Abbott RJ. Cerebral venous sinus thrombosis. *Postgrad Med J*. 2000;76:12–5.
18. Keller E, Pangalu A, Fandino J, et al. Decompressive craniectomy in severe cerebral venous and dural sinus thrombosis. *Acta Neurochir Suppl*. 2005;94:177–83.
19. Théaudin M, Crassard I, Bresson D, et al. Should decompressive surgery be performed in malignant cerebral venous thrombosis?: a series of 12 patients. *Stroke*. 2010;41:727–31.
20. Weber J, Spring A. Unilateral decompressive craniectomy in left transverse and sigmoid sinus thrombosis. *Zentralbl Neurochir*. 2004;65:135–40.
21. Boussier MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol*. 2007;6:162–70.
22. Newman CB, Pakbaz RS, Nguyen AD, et al. Endovascular treatment of extensive cerebral sinus thrombosis. *J Neurosurg*. 2009;110:442–5.
23. Aaron S, Alexander M, Moorthy RK, Mani S, Mathew V, Patil AK, Sivadasan A, Nair S, Joseph M, Thomas M, Prabhu K, Joseph BV, Rajshekhar V, Chacko AG. Decompressive craniectomy in cerebral venous thrombosis: a single centre experience. *J Neurol Neurosurg Psychiatry*. 2013;84(9):995–1000. <https://doi.org/10.1136/jnnp-2012-303356>.
24. Zuurbier SM, Coutinho JM, Majoie CB, Coert BA, van den Munckhof P, Stam J. Decompressive hemicraniectomy in severe cerebral venous thrombosis: a prospective case series. *J Neurol*. 2012;259(6):1099–105. <https://doi.org/10.1007/s00415-011-6307-3>.
25. Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, Derex L, Lichy C, Masjuan J, Massaro A, Matamala G, Poli S, Saadatnia M, Stolz E, Viana-Baptista M, Stam J, Boussier MG, Second International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT 2) Investigators. Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. *Stroke*. 2011;42(10):2825–31.

26. Pfefferkorn T, Eppinger U, Linn J, et al. Long-term outcome after suboccipital decompressive craniectomy for malignant cerebellar infarction. *Stroke*. 2009;40:3045–50.
27. Jüttler E, Schweickert S, Ringleb PA, et al. Long-term outcome after surgical treatment for space-occupying cerebellar infarction: experience in 56 patients. *Stroke*. 2009;40:3060–6.
28. Kase CS, Williams JP, Wyatt DA, et al. Lobar intracerebral hematomas: clinical and CT analysis of 22 cases. *Neurology*. 1982;32:1146–50.
29. Fujitsu K, Muramoto M, Ikeda Y, et al. Indications for surgical treatment of putaminal hemorrhage. Comparative study based on serial CT and time-course analysis. *J Neurosurg*. 1990;73:518–25.
30. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1–5.
31. Volpin L, Cervellini P, Colombo F, et al. Spontaneous intracerebral hematomas: a new proposal about the usefulness and limits of surgical treatment. *Neurosurgery*. 1984;15:663–6.
32. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international surgical trial in intracerebral haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387–97.
33. Prasad K, Mendelow AD, Gregson B. Surgery for primary supratentorial intracerebral hematoma. A meta-analysis of 10 randomized controlled trials. *Stroke*. 2009;40:e624–6.
34. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, STICH II Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. 2013;382:397–408.
35. Auer LM, Deinsberger W, Niederkorn K, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J Neurosurg*. 1989;70:530–5.
36. Broderick JP, Brott TG, Duldner JE, et al. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987–93.
37. Zuccarello M, Brott T, Derex L, et al. Early surgical treatment for supratentorial intracerebral hemorrhage: a randomized feasibility study. *Stroke*. 1999;30:1833–9.
38. Niizuma H, Shimizu Y, Yonemitsu T, et al. Results of stereotactic aspiration in 175 cases of putaminal hemorrhage. *Neurosurgery*. 1989;24:814–9.
39. Morgan T, Awad I, Keyl P, et al. Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. *Acta Neurochir Suppl*. 2008;105:217–20.
40. Lippitz BE, Mayfrank L, Spetzger U, et al. Lysis of basal ganglia haematoma with recombinant tissue plasminogen activator (rtPA) after stereotactic aspiration: initial results. *Acta Neurochir (Wien)*. 1994;127:157–60.
41. Schaller C, Rohde V, Meyer B, et al. Stereotactic puncture and lysis of spontaneous intracerebral hemorrhage using recombinant tissue plasminogen activator. *Neurosurgery*. 1995;36:328–33.
42. Vespa P, McArthur D, Miller C, et al. Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduction of hemorrhage volume and neurological improvement. *Neurocrit Care*. 2005;2:274–81.
43. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, Mayo SW, Bistran-Hall AJ, Gandhi D, Mould WA, Ullman N, Ali H, Carhuapoma JR, Kase CS, Lees KR, Dawson J, Wilson A, Betz JF, Sugar EA, Hao Y, Avadhani R, Caron JL, Harrigan MR, Carlson AP, Bulters D, LeDoux D, Huang J, Cobb C, Gupta G, Kitagawa R, Chicoine MR, Patel H, Dodd R, Camarata PJ, Wolfe S, Stadnik A, Money PL, Mitchell P, Sarabia R, Harnof S, Barzo P, Unterberg A, Teitelbaum JS, Wang W, Anderson CS, Mendelow AD, Gregson B, Janis S, Vespa P, Ziai W, Zuccarello M, Awad IA, MISTIE III Investigators. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393(10175):1021–32.
44. Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intra-

- ventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42:3009–16. <https://doi.org/10.1161/STROKEAHA.110.610949>.
45. Hanley DF, Lane K, McBee N, Ziai W, Tuhim S, Lees KR, Dawson J, Gandhi D, Ullman N, Mould WA, Mayo SW, Mendelow AD, Gregson B, Butcher K, Vespa P, Wright DW, Kase CS, Carhuapoma JR, Keyl PM, Diener-West M, Muschelli J, Betz JF, Thompson CB, Sugar EA, Yenokyan G, Janis S, John S, Harnof S, Lopez GA, Aldrich EF, Harrigan MR, Ansari S, Jallo J, Caron JL, LeDoux D, Adeoye O, Zuccarello M, Adams HP Jr, Rosenblum M, Thompson RE, Awad IA, CLEAR III Investigators. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017;389(10069):603–11.
  46. Gaberel T, Magheru C, Parienti JJ, Huttner HB, Vivien D, Emery E. Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage: a meta-analysis. *Stroke*. 2011;42:2776–81. <https://doi.org/10.1161/STROKEAHA.111.615724>.
  47. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD, STICH Investigators. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. *Acta Neurochir Suppl*. 2006;96:65–8.
  48. Kirollos RW, Tyagi AK, Ross SA, et al. Management of spontaneous cerebellar hematomas: a prospective treatment protocol. *Neurosurgery*. 2001;49:1378–86; discussion 1386–7.
  49. Weisberg LA. Primary pontine haemorrhage: clinical and computed tomographic correlations. *J Neurol Neurosurg Psychiatry*. 1986;49:346–52.
  50. Rajshekhar V. Management of hydrocephalus in patients with tuberculous meningitis. *Neurol India*. 2009;57:368–74.
  51. Cairns H. Neurosurgical methods in the treatment of tuberculous meningitis. *Arch Dis Child*. 1951;26:376–83.
  52. Palur R, Rajshekhar V, Chandy MJ, et al. Shunt surgery for hydrocephalous in tubercular meningitis: a long-term follow-up study. *J Neurosurg*. 1991;74:64–9.
  53. Bhagwati S, Mehta N, Shah S. Use of endoscopic third ventriculostomy in hydrocephalus of tubercular origin. *Childs Nerv Syst*. 2010;26(12):1675–82.
  54. Chugh A, Husain M, Gupta RK, et al. Surgical outcome of tuberculous meningitis hydrocephalus treated by endoscopic third ventriculostomy: prognostic factors and postoperative neuroimaging for functional assessment of ventriculostomy. *J Neurosurg Pediatr*. 2009;3:371–7.
  55. Sil K, Chatterjee S. Shunting in tuberculous meningitis: a neurosurgeon's nightmare. *Childs Nerv Syst*. 2008;24:1029–32.

# Toxins and the Nervous System

# 12

Pradeep P. Nair, Jayantee Kalita, and Usha K. Misra

---

## Introduction

Acute poisoning can result in a medical emergency and account for up to 10% of admissions into hospital. It is an important cause of morbidity and mortality in India. Generally, the effects of toxins manifest in several systems in the body, including the skin, mucus membrane, the haematopoietic, hepatic, renal and nervous systems. The neurological manifestations may involve different regions and fibre tracts of the central and peripheral nervous systems. This chapter predominantly describes the effects of toxins on the nervous system.

Toxins may be classified broadly as chemical and biological. The chemical poisons can be further divided into environmental, industrial, iatrogenic and recreational. The list of neurotoxins is exhaustive, but only those of relevance in Southeast Asia are listed in Table 12.1 and their sources in Table 12.2.

---

## Chemical Toxins

### Arsenic

The word ‘arsenic’ is derived from the Persian word meaning ‘yellow orpiment’ [2]. Arsenic has been regarded as the king of poisons and the poison of kings [3]. It has long been used as an intentional poison as it is odourless and tasteless, and its acute effects may be mistaken for symptoms of cholera [4].

---

P. P. Nair (✉)

Additional Professor, Department of Neurology, JIPMER, Puducherry, India

J. Kalita · U. K. Misra

Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

e-mail: [ukmisra@sgpgi.ac.in](mailto:ukmisra@sgpgi.ac.in)

**Table 12.1** List of toxins resulting in neurological emergencies

Toxins	Subgroups
<i>Biological</i>	
Plant toxins	<i>Dhatura</i> , cocaine, opium, cannabis, strychnine
Animal toxins	Snakebite
<i>Chemical</i>	
Heavy metals	Arsenic, thallium, lead, mercury
Alcohol	Methyl alcohol, ethyl alcohol, ethylene glycol
Organophosphates	–

**Table 12.2** Toxins and their sources

Toxins	Sources	Sources in India
Arsenic	Constituent of cosmetics is used to manufacture paint, pesticides, insecticides, herbicides, wood preservatives and cotton desiccants [1], and as an additive in animal feeds. It is used to manufacture transistors, semiconductors, LASER, etc.	Folk medicine
Thallium	Rodent poisons, manufacturing of optical lenses, semiconductors, scintillation counters, low-temperature switching devices, green-coloured fireworks, imitation jewellery and as a chemical catalyst	
Lead	Paints and contaminated soil. Industries, such as smelting, battery-making, ship-building and glass manufacture are classically associated with lead exposure	‘Surma’ ( <i>kajal</i> ) (a mixture of soot and other ingredients used predominantly by women to darken the eyelids and as mascara for the eyelashes) ‘Sindoor’, a red powder (vermilion) traditionally applied at the beginning or completely along the parting-line of a married Hindu woman’s hair or as a dot on the forehead
Mercury	Used to manufacture batteries, latex paint, polyvinyl chloride and fungicides. Also used in gold mining, refining and the electrical industry	
Ethylene glycol	Found mostly in coolant mixtures, such as radiator antifreeze	
Methanol	Used as an industrial solvent, in paint, varnish, windshield-washer fluid and sometimes in moonshine	
Isopropanol	Found in rubbing alcohol (70%), some cleaning products and many personal hygiene products	

Bangladesh and the adjoining districts of West Bengal and Uttar Pradesh in India are among the regions in the world most affected by environmental arsenic poisoning [5]. Arsenic is a constituent of cosmetics and is used in the manufacture of paints, pesticides, insecticides, herbicides, wood preservatives and cotton desiccants [6]. It is also used as an additive in animal feeds and in the manufacture of transistors, semiconductors, laser, etc. Arsenic is used in both folk and modern medicine, and has had a therapeutic role in the treatment of acute promyelocytic leukaemia relapse [1, 7]. Arsenic exposure occurs from inhalation and absorption through the skin, mucosa and gastrointestinal tract, primarily via the small intestine.

### Acute Poisoning

Most cases of acute poisoning result from an accidental exposure, attempted suicide or homicide. Small amounts (<5 mg) cause diarrhoea and vomiting, which generally resolves without treatment [8]. A lethal dose ranges from 100 to 300 mg, and death may occur within 24–96 h [9].

The clinical manifestations of arsenic poisoning involve virtually every body system. Prominent symptoms include nausea, vomiting, colicky abdominal pain, excessive salivation, and profuse watery diarrhoea resembling acute cholera [6]. The most common neurological manifestation is peripheral neuropathy which may last for up to 2 years after the acute exposure. Peripheral neuropathy has also been reported in opium addiction when the opium is contaminated by arsenic [10]. The patient can develop an acute, severe, ascending type of weakness resembling Guillain–Barré syndrome (GBS) [11]. Acute psychosis, confusion, encephalopathy and seizures can also occur. The haematological manifestations, such as haemoglobinuria, disseminated intravascular coagulation, bone marrow suppression, pancytopenia and basophilic stippling of the red blood cells can indicate the diagnosis. Renal failure, respiratory failure and pulmonary oedema are other common manifestations.

### Diagnosis

Quantification and monitoring of arsenic exposure is done by analysing blood, urine and hair samples. Levels between 1 and 3 mg/kg hair sample indicate acute toxicity. Urine arsenic (collected in metal-free containers) of >50 µg/L or 100 µg/24 h also suggests acute poisoning.

### Treatment

#### Acute Arsenic Poisoning

**General Measures** The primary concern is to correct dehydration and restore vital body functions. Gastric lavage, activated charcoal and haemodialysis (HD) may be considered to increase elimination of the toxin from the body. The efficacy of these detoxification methods, however, has not been well documented.

**Specific Measures** For treatment of acute arsenic poisoning, the chelator 2, 3-dimercapto-L-propanol (British anti-Lewisite [BAL]), has been used with successful results [12]. Oral anti-arsenic drugs, such as meso-2, 3-dimercaptosuccinic acid (DMSA) and sodium-2, 3-dimercapto-L-propamesulfonate (DMPS) may not be easily available in India.

The neurological complications, such as distal symmetrical sensory axonal neuropathy, are late effects of acute arsenic poisoning. These neurological deficits generally do not respond to chelation therapy [13].

## Thallium

Thallium is a colourless, tasteless and odourless heavy metal. It is used in rodent poisons and in the manufacture of optical lenses, semiconductors, scintillation counters, low-temperature switching devices, green-coloured fireworks, imitation jewellery and as a chemical catalyst. Thallium is highly toxic to humans, with a fatal dose of 10–15 mg/kg body weight [14].

The strict regulation of thallium use has diminished to a large extent both industrial and intentional thallium poisoning. However, the physical properties of thallium salts lead to a high potential for misuse. The manifestations of thallium poisoning may be similar to arsenic poisoning in the early stage and can be confused with GBS, porphyria, myocardial infarction, diabetic neuropathy, systemic lupus erythematosus, and carbon monoxide and organophosphate poisoning [14–16]. Although thallium poisoning occurs commonly after oral ingestion, it can ‘also occur after inhalation of contaminated dust or after dermal absorption’ [14].

## Clinical Features

Early GI symptoms of toxicity are vague and include abdominal pain, nausea and vomiting. Hepatic, renal and haematological toxicity also occur [17]. The cardiovascular system is the main target of thallium toxicity in the early stage, and results in tachycardia and hypertension. Neurological symptoms, such as paraesthesia and allodynia, are acute manifestations and not consistent with typical polyneuropathy. The severe limb pain with preservation of the proximal limb reflexes helps to distinguish it clinically from GBS [15, 17]. Thus, neurological symptoms may represent some of the earliest and most useful findings in the early stages of thallium poisoning and may affect both central and peripheral nervous systems. [18] CNS symptoms may include somnolence, hallucinations, tremor, ataxia, athetosis, seizures or even death [19]. Paraesthesia, dysaesthesia, allodynia and severe pain are the most common features of involvement of the peripheral nervous system [20]. The clinical manifestations of thallium poisoning depend on the quantity consumed and the route of exposure. The tendon reflexes may be reduced [15], normal [17] or exaggerated [21]. The typical clinical picture unfolds by 2–3 weeks of acute poisoning, especially with the development of alopecia, which is a characteristic feature of thallium poisoning (Fig. 12.1). Ironically, by this time the critical time for therapeutic intervention is lost.

**Fig. 12.1** Thallium poisoning—alopecia on the 45th day



## Treatment

**General Measures** Because of the rarity of thallium poisoning, treatment algorithms are limited. The use of HD is controversial. Misra et al. [22] reported improvement after HD in one patient. Lu et al. [23] also found that the urinary thallium levels seemed to decrease rapidly during HD. Forced diuresis is often employed, but its benefit is questionable [24].

**Specific Measures** Prussian blue, a crystal blue lattice of potassium ferric ferrocyanide, is regarded as the treatment of choice for thallium poisoning. It acts by forming a non-absorbable complex with thallium, which interrupts its enterohepatic recycling and increases its excretion. Both potassium supplementation and B complex administration are also potentially useful measures suggested by the putative pathophysiological mechanisms of thallium toxicity. Potassium administration is proposed to increase thallium mobilization from tissue stores (hence, its availability for glomerular filtration) and compete with it at the level of the renal tubule. Although excretion is indeed enhanced after potassium treatment, clinically, potassium supplementation produces a transient worsening of the underlying neurological symptoms. Hence, this treatment modality is not recommended.

## Lead

Lead exists in elemental inorganic and organic forms. The common sources of inorganic lead include paints and contaminated soil. Industries, such as smelting, battery-making, ship-building and glass manufacture are classically associated with lead exposure. *Surma (kajal)* is a mixture of soot and other ingredients used predominantly by women in the Middle East, North Africa, the Horn of Africa and South Asia to darken the eyelids and as mascara for the eyelashes. Mothers traditionally have applied *surma* to their infants' eyes soon after birth as a tradition to 'strengthen the child's eyes', and/or to protect the child from the 'evil eye'. This has



been reported to produce lead encephalopathy in children; many *surma* samples contain as much as 88% lead sulphide. In India, silver refining—in which equal amounts of lead and silver are mixed and boiled in a hand-operated furnace—is a key source of occupational lead poisoning. On cooling, the lead separates leaving pure silver behind. In the process, the workers inhale lead fumes and develop lead poisoning. The lead is absorbed by the gastrointestinal tract and lung. Lead poisoning has also been reported in painters.

Lead inhibits sulphhydryl-containing enzymes, acts as an inhibitor or agonist of calcium-dependent processes and inhibits haem synthesis. The clinical picture of lead poisoning may thus simulate acute porphyria because of the identical biochemical changes.

### Clinical Features

Acute lead intoxication is uncommon, but can occur from inhalation of large quantities of lead fumes; in children, lead intoxication can result from ingestion of lead-based foreign bodies. Characteristics of acute lead poisoning include abdominal colic, constipation, anaemia, fatigue, renal failure, peripheral neuropathy and, in severe cases, encephalopathy with coma, convulsions and papilloedema. Lead produces pure motor neuropathy resulting in foot drop or wrist drop.

### Diagnosis

Measurement of blood lead levels is the standard screening test for toxicity. Normally, blood levels are  $<10 \mu\text{g/dL}$ . Normocytic anaemia with basophilic stippling of the RBCs and abnormal liver functions are additional findings.

### Treatment

**General Measures** Gastric lavage should be undertaken for a recent ingestion. Whole bowel irrigation is recommended for ingestion of lead. Activated charcoal does not bind lead. Seizures may not respond to benzodiazepines and in such cases measures to reduce the intracranial pressure may be tried.

**Specific Measure** If the blood lead level is  $>70 \mu\text{g/dL}$  in children or  $>100 \mu\text{g/dL}$  in adults, the current recommendation for chelation of lead is to use a combination of intramuscular British anti-Lewisite (BAL) and intravenous calcium disodium edetate. The treatment is continued for 5 days and the course of calcium edetate is repeated every 2–5 days. DMSA is effective both in children and adults. It is recommended if the blood lead level is  $45\text{--}69 \mu\text{g/dL}$  in children or  $70\text{--}100 \mu\text{g/dL}$  in adults, provided serious side-effects such as encephalopathy are not present. D-penicillamine is recommended in a dose of  $25\text{--}40 \text{ mg/kg}$  four times a day orally for 1–6 months.

### Mercury

Mercury occurs in nature in its elemental state, and organic and inorganic salts. Elemental mercury readily vaporizes at  $0^\circ\text{C}$  and can result in significant

concentration when kept in an open container in a poorly ventilated room. Mercury is used to manufacture batteries, latex paint, polyvinyl chloride and fungicides. It is also used in gold mining, petroleum refining and the electrical industry. The organic salts of mercury have medicinal value and are widely used as topical antiseptics. Industrial discharge into rivers and streams results in contamination of seafoods and freshwater fish, which become important sources of mercury poisoning (Minamata disease).

After inhalation, 80% of elemental mercury gets absorbed from the lungs and can cross the blood–brain barrier (BBB). After absorption it is rapidly oxidized into inorganic mercury, which does not cross the BBB effectively.

### Clinical Features

Oral or parenteral ingestion of elemental mercury and acute organic and inorganic mercury poisoning are less likely to produce neurological manifestations. Acute inhalation of elemental mercury results initially in pulmonary toxicity causing cough, haemoptysis, tachycardia, cyanosis and death. Gastrointestinal manifestations include diarrhoea, vomiting, salivation and dysphagia. If a patient survives this stage, headache, blurred vision and encephalopathy develop. Some of the survivors may also develop tremors, renal dysfunction and gingivostomatitis, which are the usual manifestations of chronic exposure to elemental mercury.

### Diagnosis

For poisoning with elemental mercury, mercury salts and methyl mercury, the whole blood mercury level reflects very recent exposure, whereas urine and hair may be tested for chronic exposure. The normal level of mercury in blood is <10 µg/L.

### Treatment

**General Measures** Acute mercury poisoning is best managed by discontinuing the exposure and providing supportive care. Oxygenation, assisted ventilation, surgical removal of the metal from the intestines and subcutaneous tissue may be required. Haemodialysis may be useful in inorganic mercury ingestion and gastric lavage is recommended for ingestion of organic mercury salts.

**Specific Measures** Chelation therapy should be started regardless of the suspected form of mercury. DMSA is the most effective drug for both elemental and inorganic mercury poisoning, as it is effective, has low toxicity and can be used orally. It is administered at a dose of 10 mg/kg 8 hourly.

### Organophosphates

Organophosphate compounds are the organic derivatives of the phosphorus-containing acids; they act as anti-cholinesterases.

Acute organophosphate toxicity is an important cause of morbidity and mortality, particularly in developing countries. According to WHO, there are one million

serious accidental and two million suicidal poisonings annually worldwide. These are caused by insecticides, 2,00,000 of which result in death, with most of the deaths occurring in developing countries [25]. Although the exact statistics are not available for India, hospital-based studies suggest that organophosphates are the commonest poisons and account for nearly half of the poisoning cases admitted to emergency wards. Most of these poisonings are with suicidal intent [26–28].

### **Mechanism of Toxicity**

The toxic effects of organophosphates occur after absorption from the skin, mucus membrane and respiratory tract after accidental exposure or suicidal ingestion. After hydrolysis by esterases, organophosphates bind to a number of enzymes in the body, of which the reaction with acetylcholine esterase is clinically significant. Organophosphates phosphorylate acetylcholine esterase and inhibit its normal action. The bond between the phosphorus atom and the esteratic site on the enzyme is stable and takes hours to week(s) to break. The recovery of the enzyme occurs at a rate of about 1% per day [29]. Studies have shown that a phenomenon of enzyme ageing occurs, which involves the cleavage of the radical from the inhibited enzyme, making it resistant to rephosphorylation. The net result is the accumulation of acetylcholine at nerve endings resulting in nicotinic and muscarinic over activity.

### **Clinical Features**

Organophosphate poisoning produces three well-defined clinical syndromes:

1. Initial acute cholinergic crisis
2. Intermediate syndrome
3. Delayed polyneuropathy.

### **Cholinergic Crisis**

The symptoms result from a mixture of the muscarinic (post-ganglionic parasympathetic), nicotinic (neuromuscular junction) and CNS effects of acetylcholine excess. The muscarinic symptoms include diarrhoea, salivation, lacrimation, bronchorrhea, bronchospasm, bradycardia and miosis. Overactivity of the nicotinic receptors can result in hypertension and tachycardia in place of hypotension and bradycardia. Nicotinic overactivity also results in muscle paralysis and fasciculations. Progressive muscle weakness may culminate in respiratory paralysis.

The CNS manifestations of organophosphate poisoning include irritability, mental obtundation, coma and convulsions. Although the paralysis usually passes off within 48–72 h, complete recovery may occur only over days.

### **Investigations**

Electrophysiological studies soon after the exposure show repetitive discharges after a single evoked compound motor unit potential and a decrement increment response at high-rate repetitive nerve stimulation (RNS) [30]. As the degree of the muscle weakness progresses, the repetitive discharges disappear and decremental response can be elicited at a low-rate RNS. A study of single-fibre electromyogram

(EMG) showed increased jitter in patients exposed to organophosphate compounds [30], which can be demonstrated even before the decremental response is elicited with tetanic stimulation. This abnormality of impulse transmission persists long after recovery from the cholinergic crisis.

### Intermediate Syndrome (IMS)

The IMS from organophosphate poisoning was first reported by Senanayake and Karalliedde [31]. The reported incidence is between 20% and 68% [32] and it occurs 12–96 h after exposure to the toxin. The IMS results from prolonged action of acetylcholine at the nicotinic receptors; it manifests as paralysis of the ocular, bulbar, neck, proximal limb and respiratory muscles. Occurrence of respiratory paralysis may be the first clue to IMS. The paralysis is purely motor and full recovery occurs within 4–18 days. In a review of 19 cases of IMS after organophosphorus ingestion, the authors showed a decremental response at low or intermediate frequencies [31]. The decremental responses were maximal for the second response, with a gradual but incomplete recovery by the ninth response. The EMG findings in this syndrome are suggestive of a combined pre- and post-synaptic defect [31].

## Treatment

### Cholinergic Crisis

**General Measures** The treatment of cholinergic crisis begins with skin and gastrointestinal decontamination. Adequate oxygenation should be ensured.

### Specific Measures

**Atropine** Atropine is used to counter the muscarinic effect of acetylcholine in a dose of 2–4 mg i.v. every 10–15 min until complete atropinization is achieved and this state is maintained for 3–5 days. Atropinization is evidenced by dry skin, pulse rate of >100/min, pupillary dilatation and drying up of secretions. Studies on the management of organophosphorus poisoning have shown the beneficial effect of continuous i.v. infusion of atropine at a rate of 0.02–0.08 mg/kg/h, compared with intermittent administration [33]. Atropine has also been shown to have a beneficial effect on the neuromuscular junction by acting at the inhibitory presynaptic muscarinic receptors.

**Oximes** During the cholinergic crisis, oximes have been used as rejuvenators of acetylcholine esterase. However, their usefulness is controversial. Some studies have shown the formation of a potent phosphorylated oxime, which acts by directly detoxifying the unbound organophosphorus compound and by cleavage of the phosphorylated site [34].

The dose of pralidoxime is 1 g i.v. 8 hourly; continuous infusion at a dose of 500 mg/h is also recommended in severe poisoning. The toxicity of pralidoxime is evidenced by circumoral paraesthesia, convulsions and neuromuscular paralysis. Studies have shown some beneficial effect of magnesium in organophosphorus

poisoning by preventing ventricular arrhythmia and even reversing the neuromuscular block [35]. However, more studies are required before recommending the routine use of magnesium. Supportive measures, such as fluids, electrolytes, ventilatory support, and control of caloric intake, temperature, seizures and secondary infection are important in the management of IMS. Atropine is of no benefit in this situation.

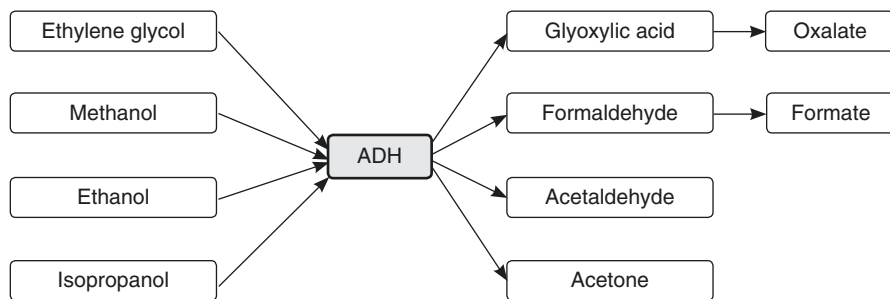
Because IMS generally concurs with severe organophosphate toxicity and persistent inhibition of acetylcholinesterase, it has no specific therapy. Early aggressive decontamination, appropriate antidote therapy and prompt institution of ventilatory support may be helpful in ameliorating the magnitude and/or the incidence of IMS. The prognosis of IMS, however, is likely to be favourable if respiratory failure can be recognized early and treated promptly [35].

## Alcohol Poisoning

The three most common toxic alcohols ethylene glycol, methanol and isopropanol follow a common metabolic pathway via the enzyme alcohol dehydrogenase (ADH) (Fig. 12.2). Thus, therapeutic measures can be initiated to block ADH with enzyme-blocking agents, or by substituting substrate with ethanol, and preventing the development of acidosis and toxic metabolites.

### Ethylene Glycol

Ethylene glycol is found mostly in coolant mixtures, such as radiator antifreeze. As it has a sweet taste, animals and young children might consume considerable amounts of this poison. It has a short half-life of approximately 3 h, so initial and 6-h serum electrolytes and serum osmolality are sufficient to rule out serious toxicity. ADH metabolizes ethylene glycol to glycolaldehyde, which is then further metabolized by aldehyde dehydrogenase into glycolic acid. Glycolic acid is further metabolized into glyoxylic acid and finally into either glutamate or  $\alpha$ -ketoadipic acid or extremely toxic oxalate metabolites.



**Fig. 12.2** Metabolic pathway for alcohols via ADH

### Clinical Features

Alcohol toxicity follows a three-phased pattern clinically. In the first 12 h post-ingestion, neurological and gastrointestinal symptoms predominate and nausea, vomiting and drowsiness may be observed. A few patients may become comatose. In the second phase (between 12 and 24 h post-ingestion), organic acid accumulation leads to tachycardia, pulmonary oedema, hypocalcaemia and metabolic acidosis. The third phase consists of acute tubular necrosis and renal failure, and begins 24 h post-ingestion [36].

### Treatment

The management of alcohol poisoning is detailed later. The general principles of management include supportive care, ADH blockade with ethanol or fomepizole (4-methylpyrazole), and dialysis [37].

### Methanol

Methanol is used as an industrial solvent in paint, varnish, windshield-washer fluid and sometimes in moonshine. Poisoning generally results from accidental ingestion of products containing methanol, or ingestion as a method of attempting suicide, or when it is taken in lieu of ethanol when the latter is in short supply [37, 38]. Methanol has a half-life of 8 h, which is longer than the other toxic alcohols. It is absorbed rapidly after ingestion and metabolized to formaldehyde by ADH. Methanol levels peak at 30–90 min post-ingestion. Aldehyde dehydrogenase rapidly metabolizes formaldehyde into formic acid, a highly toxic metabolite. The formate accumulates in the body resulting in a metabolic acidosis, in addition to neurological and ophthalmological manifestations. In the presence of folate, formic acid is reduced to carbon dioxide and water [39].

The quantity of methanol that produces toxicity ranges from 15 to 600 mL, depending on the concentration [40]. If left untreated or if treatment is begun after the full-blown syndrome has developed, mortality can be higher. Overall mortality in three studies with more than 400 patients varied between 8% and 36%, but increased to 50%–80% when serum bicarbonate concentration was <10 mEq/L and/or blood pH was <7.1 when treatment was begun [41, 42].

### Clinical Features

Visual disturbances, including decreased visual acuity, photophobia, blurred vision and abdominal pain, are the most common symptoms of methanol intoxication, with either one or both being found in 37%–72% of patients. Abdominal pain can be present both in the presence and absence of pancreatitis [41].

Hyperaemia of the optic discs and a reduced pupillary response to light may be present. Although most patients will recover normal visual function, permanent impairment of vision has been reported in 11%–18% of patients [37, 41].

Neurological abnormalities, including confusion, stupor and coma, are often present [40]. The severity of the neurological and visual dysfunction increases with the severity of metabolic acidosis [37, 41]. Rarely, methanol intoxication results in

putaminal necrosis, which manifests with parkinsonian features, such as rigidity, tremor and monotonous speech. It has been attributed to reduced cerebral blood flow and/or accumulation of formic acid in the putamen [39]. The syndrome often resolves, but sometimes neurological abnormalities can persist. Kussmaul breathing, impaired cardiac function and hypotension resulting from acidemia are most profound when the blood pH is  $<7.2$  [42]. The clinical findings in methanol intoxication often develop in a characteristic manner. Mental changes with methanol poisoning are present within the first 6–24 h but can be the only abnormality for as long as 72–96 h if patients have also ingested ethanol [39–41]. The absence of more prominent signs or symptoms at this stage can delay the diagnosis. As methanol is metabolized to formic acid, visual and more severe neurological abnormalities become prominent [39, 41, 43–45].

### Treatment

See below.

### Isopropanol

Isopropanol is found in rubbing alcohol (70%), some cleaning products and many personal hygiene products. This alcohol produces an intense inebriation and more severe respiratory and neurological depression than the other two toxic alcohols. Gastritis is a frequent clinical finding in isopropanol poisoning. Isopropanol is readily absorbed through the gastrointestinal tract and, unlike the other alcohols, toxicity can result from excessive dermal exposure. About 30% of isopropanol is excreted unchanged through the kidney, while ADH metabolizes the other 70% into acetone, which is excreted through the lungs or the kidneys.

### Treatment

**General Principles of Management of Alcohol Intoxication** Absorption from the gastrointestinal tract is rapid; therefore, gastric lavage, induced emesis or use of activated charcoal must be initiated within 30–60 min of ingestion to be beneficial. Administration of ethanol or fomepizole to attenuate the metabolism of alcohol is an integral part of therapy. Although ethanol has never been approved by the US Food and Drug Administration for this purpose, it has been used in the treatment of methanol and ethylene glycol intoxication for many years [39, 40]. Ethanol has 10–20 times greater affinity for ADH than the other types of alcohol; it completely inhibits ADH at a serum concentration of 100 mg/dL [46]. Since ethanol is cleared by dialysis, the dosage has to be increased in patients undergoing dialysis. Fomepizole has 500–1000 times greater affinity for ADH than ethanol and can completely inhibit ADH at a much lower serum concentration [39, 47]. Although it is effective when given orally, it is available only as an i.v. preparation [39, 48]. Studies in humans have confirmed its effectiveness in preventing metabolism of methanol and ethylene glycol to their toxic by-products [39, 48]; consequently, it is approved for the treatment of both intoxications. The advantages and disadvantages of both ethyl alcohol and fomepizole are given in Table 12.3.

**Table 12.3** Comparison of fomepizole and ethanol for the treatment of alcohol poisoning

Compound	Advantages	Disadvantages
Fomepizole	<ol style="list-style-type: none"> <li>1. High affinity for alcohol dehydrogenase (500–1000 times more than ethanol)</li> <li>2. Effective at relatively low serum concentrations</li> <li>3. Minimal adverse effects</li> <li>4. No effect on mentation that could confuse interpretation of clinical course</li> <li>5. Constant monitoring of blood levels not necessary</li> <li>6. Hospitalization in intensive care unit not necessary</li> <li>7. No increase in serum osmolality</li> </ol>	<ol style="list-style-type: none"> <li>1. Not available in all clinical settings</li> <li>2. Expensive</li> <li>3. Only intravenous preparation available</li> </ol>
Ethanol	<ol style="list-style-type: none"> <li>1. Inexpensive</li> <li>2. Can be given intravenously or orally</li> </ol>	<ol style="list-style-type: none"> <li>1. Available in most clinical settings</li> <li>2. Needs relatively high serum concentrations, approximately 100 mg/dL, to completely saturate the enzyme</li> <li>3. Requires constant monitoring of blood levels and possibly that of toxic alcohol</li> <li>4. Hospitalization in ICU necessary during treatment</li> <li>5. Increases serum osmolality, which can prevent effective use of serum osmolality to monitor response to therapy</li> <li>6. Impairs mentation, which can confuse interpretation of response to therapy</li> </ol>

The American Academy of Clinical Toxicology recommends ethanol or fomepizole for the treatment of methanol intoxication on the basis of the following criteria:

- Plasma methanol concentration >20 mg/dL or recent history of ingestion of methanol with serum osmolal gap of >10 mOsm/L.
- Strong clinical suspicion of methanol poisoning with at least two of the following parameters:
  - Arterial pH <7.3
  - Serum  $\text{HCO}_3^-$  < 20 mEq/L
  - Osmolal gap >20 mOsm/L [39, 46].

The American Academy of Clinical Toxicology recommends haemodialysis, which should be considered in the presence of metabolic acidosis (blood pH 7.25–7.30), visual abnormalities, renal failure or electrolyte imbalance unresponsive to conventional therapy, and/or serum methanol concentration of >50 mg/dL [39]. However, fomepizole treatment of patients with methanol



**Table 12.4** Recommended dosage of fomepizole for patients with methanol and ethylene glycol intoxication

	Loading dose	Maintenance dose
Without dialysis	15 mg/kg body weight	10 mg/kg body weight every 12 h for 4 h 15 mg/kg body weight every 12 h (if blood levels do not reach goal by 48 h)
With dialysis		Add 1–1.5 mg/kg body weight per hour

intoxication, even with serum concentrations <50 mg/dL, either eliminated completely the need for dialysis or allowed it to be done electively many hours after hospitalization (Table 12.4) [49, 50].

## Biological Toxins

### Snake Envenomation

The Indian subcontinent is home to over 230 species of snakes, of which more than 50 are venomous. Only four species were considered to be of clinical significance until recently as they are responsible for most of the annual snakebite-related deaths. However, in 2007, the Indian Government's Ministry of Health and Family Welfare rejected the notion of the 'Big Four' and instead adopted the concept as outlined in a WHO paper [51]. Elapidae (cobras and kraits) and hydrophidae (sea snake) bites result in envenomation with neurotoxicity. An estimated 35,000–50,000 people die of snakebite every year in India [52], making it the largest single contributor to the global tally of snakebites. Snakebite is an occupational hazard mainly in the rural areas with bites seen commonly on the limbs. The circumstances of the bite permit, at best, a good guess about the species involved. Krait bites are almost exclusively nocturnal, indoor, unprovoked and painless. Cobra bites are often associated with pain and local swelling, with neuromuscular paralysis in both krait and cobra bites. Sea snakes produce a painless bite with minimal local reaction but severe myalgia. Toxins from cobra venom predominantly act post-synaptically, whereas those of krait venom mainly act pre-synaptically; however, most snake venoms contain both pre- and post-synaptic neurotoxins [53].

### Clinical Features

One-third to half of the patients bitten by poisonous snakes do not develop serious effects. Before the full-blown clinical syndrome of envenomation develops, nausea, vomiting, headache, abdominal pain and fainting occur and must be regarded with the highest degree of suspicion as indicators of envenomation. Cobra bite, unlike that of the krait, is usually accompanied by pain and swelling at the site of the bite, painful regional lymphadenopathy, blister formation and tissue necrosis. The bites of elapid snakes cause prominent neurotoxicity, which manifests as paralysis of the ocular, bulbar, limb and respiratory muscles [53]. Neuromuscular paralysis usually

**Fig. 12.3** A boy showing myasthenic symptoms after snakebite: Ptosis and tongue weakness are seen



supervenes within 6 h, but may be delayed for up to 12 h. It manifests initially as bilateral ptosis, which then spreads to involve the palatal muscles, tongue, jaw, larynx, pharynx, neck and the respiratory muscles (Fig. 12.3). Consciousness is usually retained. Krait bites produce a similar clinical picture with a major exception being the absence of local reaction. The onset of paralysis is usually rapid. Elapid bites may later produce myonecrosis and coagulopathy.

### Treatment

**General Measures** The first reaction of a patient bitten by a snake is fright. Management should begin with reassurance, immobilization of the affected part to reduce muscle contraction and the flow of lymph. Incision, suction, washing, electrical and cryotherapy, and application of a tourniquet on the local wound site are all associated with increased morbidity.

An intravenous line should be inserted, tetanus toxoid should be administered and an anxiolytic and analgesic should be offered; opiates should be avoided. The patient should be observed carefully for at least 24 h for systemic envenomation.

Neostigmine is useful in the management of cobra bites. Endotracheal intubation, tracheal suctioning and mechanical ventilation are life-saving. If ventilators are not available, Ambu bag ventilation may be life-saving [54].

## Specific Measures

**Snake Antivenom (SAV)** SAV is life-saving. In India only polyvalent antivenom is available. The dose is the same for adults and children. A test dose is not required. Because the SAV is an equine serum, adverse reactions are common. However, as its benefits outweigh the side-effects, treating the reactions rather than deferring the antivenom is advisable. Adrenaline, antihistamines and steroids should be kept handy for managing the reactions.

The dose of SAV in severe neurotoxic snake envenomation should ideally be based on measuring the serial venom concentrations in the patient and determining when free venom concentrations are undetectable [55]. Clinically, this is rarely feasible. In the absence of any definite data, [56] most recommendations are based on mouse assays, in which the lethal dose is estimated to be around 120 mg of cobra venom and 60 mg of krait venom [57]. The amount of venom neutralized by 1 mL of SAV is approximately 0.6 mg and 0.45 mg for cobra and krait, respectively. Thus, empirically, the total SAV requirement for otherwise fatal cobra and krait bites is 200 and 134 mL, respectively. However, this may not be true for human snakebites, as the exact total amount of venom injected by the snake at the time of bite is variable, depending on the species and size of the snake, the mechanical efficiency of the bite, whether one or two fangs penetrated the skin, and whether repeated strikes were made. There is no consensus on the dose of SAV required in the management of snakebite, and selection of a specific dose of SAV is controversial. The antivenom is effective only if given early enough to neutralize the venom in the circulation, before the neurotoxins reach their target site. Therefore, the use of large doses late in the course of envenoming is unlikely to be effective. A single dose of 8–10 vials (10 mL vials) is usually adequate for elapid bites. Studies have failed to show any advantage of high-dose SAV over the low-dose protocol [58].

## Plant Poisons

### **Dhatura and Related Plants**

Two varieties of *dhatura* plants occur in nature, the white flowered *D. alba* and purple flowered *D. niger*. These plants are found in almost all parts of the world; in India the most common species is *D. stramonium*. Related plants include *Atropa belladonna* and *Hyoscyamus niger*. Although all parts of the plant are poisonous, the flower and the seeds are the most toxic. Each flower contains about 500 seeds; ingesting 4–5 seeds can be fatal. The toxic side-effects result from atropine, hyoscyamine and scopolamine, which produce an anti-cholinergic crisis.

### **Clinical Features**

Symptoms appear 30–60 min after ingestion and may last for up to 48 h or even for several days because of the reduced gastric motility. The mnemonic ‘hot as a hare, red as a beet, blind as a bat, dry as a bone, mad as a hatter’ has been used to describe

individuals affected by *dhatura* poisoning. Patients develop hyperthermia, flushing, mydriasis, dry skin, delirium, tachycardia and urinary retention. The delirium is described as a 'muttering' delirium. The patient becomes noisy, confused and psychotic, and has auditory and visual hallucinations, with a tendency to pick at the bedclothes and pull imaginary threads with the fingertips. The patient may also develop ataxia and extrapyramidal features. Respiratory paralysis results in death.

### Treatment

**General Measures** Gastric lavage may be useful up to 48 h after ingestion. Charcoal reduces absorption of the toxin from the gut. Benzodiazepines may be useful in controlling agitation and seizures.

**Specific Measures** Should the patient have hyperthermia, seizures and supra-ventricular tachycardia, physostigmine 1–2 mg i.v. is administered slowly over 5 min. The total dose of neostigmine should not exceed 4 mg otherwise it may precipitate seizures, cholinergic crisis and asystole.

### Cannabis

The most common species of cannabis is *C. sativa*. *C. indica* is grown in India; it is a sub-species of *C. sativa*. The alkaloids derived from the plant, collectively known as cannabinoids, are used for recreational purposes. The flowers of cannabis contain the physiologically psychoactive cannabinoid, the most active being delta-9 tetrahydrocannabinol (THC). The most commonly abused form is marijuana, which is made of the dried plant products, such as leaves, stems and seeds. It can be ingested or smoked in a cigarette. An average cigarette contains approximately 1% THC. *Hashish* or *charas*, the dried resin derived from flower tops, contains 4–15% THC. *Bhang* and *ganja* are the other abused forms of the plant.

### Clinical Features

When smoked, 50% of THC is absorbed into the bloodstream and the effects appear in minutes. Oral ingestion leads to absorption of 3–10% of THC and the effects begin in 30–60 min. The early phase is characterized by anxiety, panic and a fear of death, hyperactivity and restlessness. The latter phase is associated with a sense of well-being, euphoria and exhilaration. Patients may become drowsy and lethargic. An especially serious risk associated with acute cannabis use is cerebellar infarction [59].

### Treatment

Most frequently, the symptoms are self-limiting and no treatment is required. Diazepam or haloperidol may be used for psychotic symptoms.

### Strychnos Nux Vomica

This is an evergreen tree found in Southeast Asia and it contains the toxic alkaloid strychnine, which is one of the bitterest substances. It is also used in homeopathic and ayurvedic preparations.

Strychnine competes with glycine in the brain and blocks its post-synaptic inhibition. This disinhibition causes excessive motor neuron impulses, causing recurrent convulsions. The estimated lethal dose of strychnine is 15–30 mg.

### **Clinical Features**

Poisoning occurs after ingestion of the seeds of *nux vomica*; symptoms develop within 15–20 min. The patient initially develops twitching of the muscles, which soon progresses to convulsions, trismus and opisthotonus. These are precipitated and exaggerated by the slightest of stimuli. This condition needs to be differentiated from tetanus.

### **Treatment**

**General Measures** Prompt management is important to save the patient. Maintaining a clear airway and ventilator support is life-saving. Activated charcoal adsorbs the unabsorbed poison. All extraneous stimuli that precipitate seizures should be avoided. It is better to manage the patient in a quiet, isolated room.

**Specific Measures** Benzodiazepines are useful in treating the seizures and may have to be given as an infusion.

### **Cocaine**

Cocaine is an alkaloid derived from the leaves of *Erythroxylon coca*, which grows in South America. Worldwide, cocaine or crack is used for recreational purposes. Cocaine binds to the dopamine transporter protein and blocks it, resulting in accumulation of dopamine at the synaptic cleft, which in turn results in a prolonged post-synaptic excitation. A dose of 1–3 g cocaine can be fatal.

### **Clinical Features**

Initially, euphoria, hyperactivity, restlessness, enhanced interest in sexual indulgence and pleasure, hypertension and tachycardia are experienced, followed by depression and further craving for cocaine. Twitching, itching, paranoid behaviour, hallucinations and impotence may occur. Intense vasoconstriction may lead to hyperthermia, myoglobinuria, renal failure or stroke. Death can result from intracerebral haemorrhage, heart failure or respiratory failure.

### **Treatment**

Cocaine poisoning has no specific antidote and the patient is given supportive and symptomatic treatment. Measures are taken to prevent further absorption of the drug from the gut and to control hypertension, arrhythmia, seizures and hyperthermia.

### **Opium**

Crude opium is used widely in India as a recreational drug. It is derived from a milky fluid that exudes from the unripe seed capsules of the poppy plant *Papaver somniferum*. Crude opium ingested orally is a common cause of poisoning,

particularly in small children. The most important alkaloids in opium are codeine, morphine, noscapine and papaverine. Symptoms begin within 2–3 h of oral ingestion and peak at 6–8 h.

### Clinical Features

The classical triad of opium poisoning is pinpoint pupils, respiratory depression and coma. Tachycardia, cardiac conduction defects and cardiac arrest can also occur. Death is usually caused by respiratory depression.

### Treatment

Maintenance of the airway and ventilation are the prime concerns. The specific antidote for opium is naloxone. Repeated doses of naloxone 0.4–1.2 mg i.v. are beneficial. The rest of the treatment is supportive. Dialysis is ineffective.

## Conclusion

Many toxins affect the nervous system either directly or as a part of systemic involvement. Understanding the effects and management is therefore critical, especially with acute, severe exposure. An overview of the toxicology is presented in Table 12.5.

**Table 12.5** Summary of neurotoxins: Salient clinical features and management

Toxins	Diagnostic features	Laboratory	Management
<i>Heavy metals</i>			
Arsenic	Acute abdominal pain, profuse diarrhoea, ascending neuropathy similar to GBS	Levels between 1 and 3 mg/kg hair, urine arsenic >50 µg/L or 100 µg/24 h	BAL 300–450 mg/m <sup>2</sup> /day in six divided doses for 3–5 days deep i.m. DMSA, DMPS when not critically ill; not easily available
Lead	Abdominal colic, encephalopathy, wrist drop and foot drop	Blood lead level >10 µg/dL	BAL if level >100 µg/dL in adults and 70 µg/dL in children DMSA if 40–69 µg/dL in children and >70 µg/dL in adults (10 mg/kg 8 hourly for 5 days and then 12 hourly orally)
Thallium	Paraesthesia, allodynia, retained reflexes and later alopecia	Blood level >10 µg/L	Haemodialysis, Prussian blue
Mercury	GI symptoms, encephalopathy, tremors		DMSA
<i>Organophosphates</i>	Cholinergic crisis, intermediate syndrome		Atropine 2–4 mg every 15 min, oximes 1 g i.v. 8 hourly

(continued)

**Table 12.5** (continued)

Toxins	Diagnostic features	Laboratory	Management
<i>Alcohol</i>	Nausea, vomiting, inebriation, visual disturbances, parkinsonian features	Metabolic acidosis, increased osmolar gap	Fomepizole (15 mg/kg loading dose, 10 mg/kg every 12-h maintenance dose) i.v.
<i>Snakebite</i>	Ptosis, muscle weakness, respiratory paralysis		ASV 8–10 vials (10 mL) i.v.
<i>Plant poisons</i>			
<i>Datura</i>	Hyperthermia, tachycardia, delirium, flushing, urinary retention		Physostigmine 1–2 mg i.v. Over 5 min
Opium	Pin-point pupils, respiratory depression and coma		Naloxone 0.4–1.2 mg (repeated doses) i.v.
Cannabis	Sense of well-being, lightheadedness progressing to lethargy and drowsiness		No specific treatment
Cocaine	Euphoria, paranoid behaviour, hallucination followed by depression and craving, pleasure in sexual indulgence		No specific treatment
Strychnine	Twitching of the muscle, convulsions, opisthotonus, trismus, respiratory paralysis		Respiratory support, isolation, benzodiazepines

*GBS* Guillain–Barré syndrome, *GI* gastrointestinal, *ASV* anti-snake venom, *BAL* British anti-Lewisite, *DMSA* meso-2, 3-dimercaptosuccinic acid, *DMPS* sodium-2, 3-dimercapto-1-propamesulphonate

## References

1. Espinoza EO, Ann MJ, Bleasdel B. Arsenic and mercury in traditional Chinese herbal balls. *N Engl J Med*. 1995;333:803–4.
2. Steingass A. A comprehensive Persian English dictionary. London: Kegan Paul, Trench, Trubner and Company; 1947.
3. Vahidnia A, van der Voet GB, de Wolff FA. Arsenic neurotoxicity—a review. *Hum Exp Toxicol*. 2007;26:823–32.
4. De Wolff FA, Edelbroek PM. Neurotoxicity of arsenic and its compounds. In: Vinken DJ, Bruyn GW, editors. *Handbook of clinical neurology*. Amsterdam: Elsevier; 1994. p. 283–91.
5. Nickson R, McArthur J, Burgess W, et al. Arsenic poisoning of Bangladesh groundwater. *Nature*. 1998;395:338–9.
6. Ratnaik RN. Acute and chronic arsenic toxicity. *Postgrad Med J*. 2003;79:391–6.
7. Jing Y, Wang L, Xia L, et al. Combined effect of all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukaemia cells in vitro and in vivo. *Blood*. 2001;97:264–9.
8. Kingston RL, Hall S, Sioris L. Clinical observations and medical outcomes in 149 cases of arsenate ant killer ingestion. *J Toxicol Clin Toxicol*. 1993;31:581–91.
9. Schoolmeester WL, White DR. Arsenic poisoning. *South Med J*. 1980;73:198–208.

10. Chhuttani PN, Chopra JS. Arsenic poisoning. In: Vinken DJ, Bruyn GW, editors. *Intoxication of the nervous system. Handbook of clinical neurology*, vol. 36. Amsterdam: North-Holland/Elsevier; 1979. p. 199–216.
11. Ghariani M, Adrien ML, Raucoules M, et al. Subacute arsenic poisoning. *Ann Fr Anesth Reanim*. 1991;10:304–7.
12. Vantroyen B, Heilier JF, Meulemans A, et al. Survival after a lethal dose of arsenic trioxide. *J Toxicol Clin Toxicol*. 2004;42:889–95.
13. Perriol MP, Devos D, Hurtevent JF, et al. A case of neuropathy mimicking Guillain-Barré syndrome after arsenic intoxication. *Rev Neurol*. 2006;162:374–7.
14. Moore D, House I, Dixon A. Thallium poisoning: diagnosis may be elusive but alopecia is the clue. *BMJ*. 1993;306:1527–9.
15. Tromme I, Van Neste D, Dobbelaere F, et al. Skin signs in the diagnosis of thallium poisoning. *Br J Dermatol*. 1998;138:321–5.
16. Pau PWI. Management of thallium poisoning. *Hong Kong Med J*. 2000;6:316–8.
17. Atsmon J, Taliansky E, Landau M, et al. Thallium poisoning in Israel. *Am J Med Sci*. 2000;320:327–30.
18. Prick JGG. Thallium poisoning. In: Vinken DJ, Bruyn GW, editors. *Intoxication of the nervous system. Handbook of clinical neurology*, vol. 36. Amsterdam: North-Holland; 1979. p. 239–78.
19. McMillan TM, Jacobson RR, Gross M. Neuropsychology of thallium poisoning. *J Neurol Neurosurg Psychiatry*. 1997;63:247–50.
20. Van Kesteren RG. Thallium. In: Vinken DJ, Bruyn GW, de Wolff FA, editors. *Intoxication of the nervous system. Handbook of clinical neurology*, vol. 64. Amsterdam: North-Holland; 1994. p. 322–9.
21. Tsai YT, Huang CC, Kuo HC, et al. Central nervous system effects in acute thallium poisoning. *Neurotoxicology*. 2006;27:291–5.
22. Misra UK, Kalita J, Yadav RK, et al. Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J*. 2003;79:103–5.
23. Lu CI, Huang CC, Chang YC, et al. Shortterm thallium intoxication: dermatological findings correlated with thallium concentration. *Arch Dermatol*. 2007;143:93–8.
24. Vrij AA, Cremers HM, Lustermaans FA. Successful recovery of a patient with thallium poisoning. *Neth J Med*. 1995;47:121–6.
25. Jayarathnam J. Pesticide poisoning as a global health problem. *World Health Stat Q*. 1990;43:139–44.
26. Siwach SB, Gupta A. The profile of acute poisonings in Harayana-Rohtak study. *J Assoc Physicians India*. 1995;43:756–9.
27. Malik GM, Mubarik M, Romshoo GJ. Organophosphorus poisoning in the Kashmir Valley, 1994 to 1997. *N Engl J Med*. 1998;338:1078.
28. Karalliedde L. Organophosphorus poisoning and anaesthesia. *Anaesthesia*. 1999;54:1073–88.
29. Besser R, Vogt T, Gutmann L, et al. High pancuronium sensitivity of axonal nicotinic-acetylcholine receptors in humans during organophosphate intoxication. *Muscle Nerve*. 1991;14:1197–201.
30. Baker DJ, Sedgwick EM. Single fibre electromyographic changes in man after organophosphate exposure. *Hum Exp Toxicol*. 1996;15:369–75.
31. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides: an intermediate syndrome. *N Engl J Med*. 1987;316:761–3.
32. Leon-S FE, Pradilla G, Vesga E. Neurological effects of organophosphate pesticides. *BMJ*. 1996;313:690–1.
33. Tafuri J, Roberts J. Organophosphate poisoning. *Ann Emerg Med*. 1987;16:193–202.
34. de Silva HJ, Wijewickrema R, Senanayake N. Does pralidoxime affect outcome of management in acute organophosphorus poisoning? *Lancet*. 1992;339:1136–8.
35. Yang CC, Deng JF. Intermediate syndrome following organophosphate insecticide poisoning. *J Chin Med Assoc*. 2007;70:467–72.



36. Korabathina K, Benbadis SR, Likosky D. Methanol [eMedicine website]. Available from: [www.emedicine.com/neuro/topic217.htm](http://www.emedicine.com/neuro/topic217.htm). Accessed 4 Nov 2008.
37. Paasma R, Hovda KE, Tikkerberi A, et al. Methanol mass poisoning in Estonia: outbreak in 154 patients. *Clin Toxicol*. 2007;45:152–7.
38. Brent J, Lucas M, Kulig K, et al. Methanol poisoning in a 6-week-old infant. *J Pediatr*. 1991;118:644–6.
39. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA, American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40:415–46.
40. Bennett JL, Cary FH, Mitchell GL, et al. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. *Medicine*. 1953;32:431–63.
41. Hovda KE, Hunderi OH, Taffjord AB, et al. Methanol outbreak in Norway 2002–2004. Epidemiology, clinical features and prognostic signs. *J Intern Med*. 2005;258:181–90.
42. Liu JJ, Daya MR, Carrasquillo O, et al. Prognostic factors in patients with methanol poisoning. *J Toxicol Clin Toxicol*. 1999;36:175–80.
43. Kraut JA, Kurtz I. Use of base in the treatment of severe acidemic states. *Am J Kidney Dis*. 2001;38:703–27.
44. McMartin KE, Ambre JJ, Tephly TR. Methanol poisoning in human subjects. Role for formic acid accumulation in the metabolic acidosis. *Am J Med*. 1980;68:414–8.
45. Tephly TR. The toxicity of methanol. *Life Sci*. 1991;48:1031–41.
46. Chu J, Wang RY, Hill NS. Update in clinical toxicology. *Am J Respir Crit Care Med*. 2002;166:9–15.
47. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of methanol poisoning. *N Engl J Med*. 2001;344:424–9.
48. Megarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med*. 2005;31:189–95.
49. Megarbane B, Borron SW, Trout H, et al. Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med*. 2001;27:1370–8.
50. Hovda KE, Froyshov S, Gudmundsdottir H, et al. Fomepizole may change indication for hemodialysis in methanol poisoning: prospective study in seven cases. *Clin Nephrol*. 2005;64:190–7.
51. World Health Organization. Progress in the characterization of the venoms and the standardization of the antivenoms, vol. 58. Geneva: World Health Organization; 1981. p. 1–44.
52. Warrell DA and International Panel of Experts. WHO/SEARO guidelines for the clinical management of snake bites in the Southeast Asian region. *Southeast Asian J Trop Med Public Health*. 1999;30(Suppl 1):1–85.
53. Lewis RL, Gutmann L. Snake venoms and the neuromuscular junction. *Semin Neurol*. 2004;24:175–9.
54. Bawaskar HS, Bawaskar PH. Profile of snakebite envenoming in western Maharashtra, India. *Trans R Soc Trop Med Hyg*. 2002;96:79–84.
55. Rivière G, Choumet V, Audebert F, et al. Effect of antivenom on venom pharmacokinetics in experimentally envenomed rabbits: toward an optimization of antivenom therapy. *J Pharmacol Exp Ther*. 1997;281:1–8.
56. Warrell DA. Animal toxins. In: Cook GC, Zumla A, editors. *Manson's tropical diseases*. London: WB Saunders; 2003. p. 581–618.
57. Bawaskar HS. Snake venom and antivenom: critical supply issues. *J Assoc Physicians India*. 2004;52:11–3.
58. Agarwal R, Aggarwal AN, Gupta D, et al. Low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenoming. *Emerg Med J*. 2005;22:397–9.
59. Geller T, Loftis L, Brink DS. Cerebellar infarction in adolescent males associated with acute marijuana use. *Pediatrics*. 2004;113:e365–70.

# The Problem of Death in Critical Care Medicine

# 13

David W. Crippen

---

## What Is 'Death', and Why Does It Matter?

Treatment plans in critical care medicine have pushed the envelope of debilitating disease by reversing organ dysfunction before it proceeds to organ failure. For a select population of patients with a strong potential for reanimation, such care plans have been remarkably successful. However, because the patient is given the benefit of any doubt regarding the possibility of resuscitation, critical care sometimes fails to reanimate an acceptable quality of life, creating dependence on life-supporting technology [1]. Critical care life-support systems are quite capable of, and even effective in, supporting isolated organ systems, even in the presence of brain death.

Before the post-modern technological revolution, the determination of death was simple: A patient was dead when his or her physician said he or she was dead. No one timed death because it did not matter. Death was a terminal event. There was never any intent to reverse it. However, the age of organ transplantation has radically changed the entire concept of death. We, as a society, have decreed that a person can be dead but the corpse still contain otherwise viable organs. Rather than death being defined as 'irreversible loss of cellular function' (a definition that would involve a putrefaction), death became modified to 'irreversible cessation of the integrated functioning of the organism as a whole' [2].

The brain has been defined as the primary integrator of the organism as a whole. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research [3] defines integration as 'brain function that manifests as physiologic homeostasis'. Thus when the brain dies, the rest of the body experiences a loss of integration and can be considered a shell of

---

D. W. Crippen (✉)

Departments of Emergency Medicine, Critical Care Medicine and Neurological Surgery  
University of Pittsburgh Medical (UPMC),  
Pittsburgh, PA, USA  
e-mail: [CripDW@upmc.edu](mailto:CripDW@upmc.edu)

organs functioning in purposeless disharmony. This rather complex definition simply means that when the entity that integrates the rest of the organism (the brain) dies, the organism dies with it, even though some of the cellular or tissue components within may remain independently viable if maintained by life-support systems.

Death of the whole organism is not required for the organism to be pronounced dead; only the brain need be dead [4]. Without this definition, the industry of organ transplantation would be impossible because putrefaction of the whole organism would be the only benchmark of death. The clinical determination of brain death was first described in 1957 [5]. The Harvard Medical School published its criteria for brain death in 1968, shortly after the first heart transplantation was performed [6]. Numerous other criteria followed [6–9]. The first nation to adopt brain death as the definition of legal death was Finland in 1971. There is controversy regarding the point at which the brain is ‘dead enough’ to meet the criteria for the dead donor rule [10]. Accordingly, ‘brain death protocols’ have evolved to medically and legally identify patients dead enough to bury, but with organs viable enough for transplantation. The Uniform Determination of Death Act (UDDA), promulgated in 1981, has served as a model statute for American states adopting legislation defining death [11]. The Act asserts two possible definitions of death: ‘An individual who has sustained either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem, is dead’.

---

## Relevant Brain Anatomy and Physiology [12]

The primary ventilatory centre is located in the reticular core of the medulla oblongata. A stimulus to ventilate is fired off when the blood  $p\text{CO}_2$  reaches and surpasses the ventilatory threshold. After ventilation occurs, carbon dioxide is exhaled and the  $p\text{CO}_2$  drops below the threshold. The cycle is repeated at regular intervals as the  $p\text{CO}_2$  rises and dips. This is how mammals ventilate without thinking about it, mainly during sleep. In whole brain death, spontaneous respiration does not occur even when arterial carbon dioxide ( $\text{CO}_2$ ) tension reaches 55–60 mmHg, or when the cough reflex is vigorously stimulated. The neurons that control arterial circulation are distributed diffusely in the pontine and medullary reticular core. In brain death, autonomic reflex loops may take over to regulate the arterial tension and heart rate. Therefore, changes in the arterial blood pressure and heart rate are not used as measures of brain stem function.

Pupillary reflexes are mediated through cranial nerves II and III nuclei in the midbrain. The oculocephalic (‘doll’s eye’) and vestibulo-ocular (‘cold caloric’) responses are mediated by the same reflex arc via cranial nerves VIII, III and VI, as well as the paramedian pontine reticular formation within the pons. These cranial nerve nuclei all lie adjacent to the reticular activating system (RAS), which spans the midbrain and pons. The RAS is necessary for consciousness and activation of the cerebral cortex. The RAS cannot be objectively evaluated

directly, so the adjacent cranial nerve nuclei are an indirect measure of its viability. If all the adjacent cranial nerve nuclei demonstrate failure, there is no significant possibility that the RAS is viable.

The sympathetic and parasympathetic nerve centres reside within the brain and each impacts the function of the other. The absence of an increase in the heart rate after an intravenous injection of a variable amount of atropine confirms the absence of vagal tone, which would result in de-modulation of the sympathetic centres, increasing the heart rate. By itself, the atropine test is insufficient as the sole confirmation of brain death as it may interfere with pupillary reactions. The test should be performed only after completion of clinical examination. It is not valid in patients following cardiac transplantation.

---

## Brain Death as Clinical Death

Before the advent of technological resuscitation methods, it could be said that a person was dead when the heart and lungs ceased functioning. This view no longer holds because selected organ systems can be artificially supported with modern critical care techniques, such as mechanical ventilation. The evolution of life-support systems capable of prolonging death indefinitely necessitated a more eclectic definition of death, which arrived in 1968 with the formulation of the Harvard criteria [13]. In essence, these criteria considered the irreversible loss of certain organ functions, rather than whole-body metabolic cessation, to be indicative of death. When the Harvard criteria were met, death was inevitable, even with continuing treatment. The Harvard criteria objectified death in the presence of functioning organs, opening the door for organ donation.

---

## Brain Death: Philosophy Impacts Practice

Brain death is defined as the irreversible cessation of the organism as a whole (not the whole organism) [14]. Brain death may be caused by either of two mechanisms: global injury to the entire brain or focal brain stem injury. Global brain injury may be caused by anoxia from various aetiologies, including respiratory or circulatory failure (cardiac arrest included). Focal injury of the brain stem may be primary (trauma, ischaemia, haemorrhage) or secondary (herniation of the brain downward onto the brain stem resulting from mass effect). Masses may include neoplasms, ischaemia, oedema and haemorrhage.

As previously discussed, this definition opens the door for organ donation as the person may be legally dead, but may still contain isolated viable organs. You will note that the term 'brain' is not defined. Several distinctions may be drawn. For the purposes of this discussion, the lengthy (and controversial) differentiation between whole brain death, cortical death and brain stem death will not be explored. The clinical criteria for brain death in the USA do not require measurement of cerebral

cortical function and thus do not make a physiological distinction between brain death and brain stem death.

---

## Important Distinctions [15]

Brain death necessarily entails failure of the brain stem, the home of circulation and ventilatory homeostasis. The clinical result is the same: A loss of integrative activity. That said, other impaired conditions of consciousness and homeostasis must not be confused with brain death. These other conditions are defined here.

‘Coma’, an unconscious state in which there is no response to stimuli, is not brain death. Coma can be caused by either impairment of the appropriate brain stem nuclei impacting the midbrain and pons reticular formation (intracranial haemorrhage, stroke) or impairment of the cerebral cortices of both cerebral hemispheres (metabolic derangement, ketoacidosis). Unlike brain death, which is irreversible, coma in many cases is reversible. Patients who fulfil the clinical criteria for brain death have no prospect of survival independent of artificial respiratory and circulatory support, no prospect of recovery of brain function and no prospect of improvement, even to a comatose state or a persistent vegetative state.

Persistent vegetative state (PVS) is a condition in which the brain stem continues to function after the cerebral cortices have failed. PVS is the functional opposite of brain stem death. The respiratory and circulatory systems of a patient in a PVS continue to function as the brain stem is preserved. PVS patients may have preserved sleep–wake cycles and other brain stem functions. PVS, in which there is cerebral death, has not been universally accepted as equivalent to death, whereas whole brain death has.

The ‘locked-in syndrome’ is a condition in which the lower brain stem functions (respiration, circulation, relaying of motor tracts) are impaired, while the upper brain stem functions (consciousness) remain intact. The symptoms include anarthria, quadriplegia and horizontal gaze paresis caused by an insult to the pons. Consciousness is preserved because most reticular formation fibres lie more dorsally in the pontine tegmentum. Vertical eye motion is preserved since the vertical gaze centre (rostral interstitial nucleus of the medial longitudinal fasciculus) is found in the midbrain. Consciousness is not disturbed, but this disorder can easily be misconstrued as coma since there is a near-complete deprivation of voluntary activity. Other than the potential for some limited eye movements, the patient cannot ventilate or move any skeletal muscle. Consciousness can be determined only by examination of voluntary eye movements to command and/or EEG. Axonal variants of the Guillain–Barré syndrome can mimic the locked-in syndrome.

Profound hypothermia, whether accidental or iatrogenic, may have clinical manifestations identical to those of brain death. A diagnosis of brain death can, therefore, not be made unless the core temperature is at least 32 °C. Some

sedating drugs taken in large quantities (e.g. barbiturates, benzodiazepines) have the potential to promote clinical somnolence sufficient to interfere with the evaluation of consciousness. A toxicology screen is, therefore, mandatory in any brain death examination.

---

## Clinical Diagnosis of Brain Death

The following preconditions must be met for a clinical diagnosis of brain death [2].

The cause of injury must be known. It is extremely important for there to be clear evidence of an acute, catastrophic, irreversible brain injury. There must be clear, objective evidence of brain injury on CAT or MRI of the brain that is compatible with the physical examination. A physical examination compatible with brain death is by itself insufficient.

Reversible conditions that may confuse the clinical diagnosis of brain death include hypothermia (body temperature must be  $>32^{\circ}\text{C}$ ), drug intoxication, inadvertent neuromuscular blockade, hypoperfusion and shock.

---

## The Physical Examination

The physical examination to confirm a diagnosis of brain death should be characterized by the following:

- No response to verbal or visual commands
- No spontaneous ventilation
- No spontaneous musculoskeletal movements in response to pain
- Pupils fixed and non-reactive
- No oculoccephalic reflex
- Negative oculovestibular reflex
- No corneal reflex
- No gag or cough reflex
- No ventilatory reflex at a  $\text{pCO}_2$  of 60 torr or more
- No significant heart rate increase after intravenous administration of atropine.

Normally, two separate examinations are done, one by a neurologist or neurosurgeon and the other by a critical care specialist or anaesthesiologist with experience in critical care. If, after this extensive clinical examination, the patient shows no sign of neurological function and the cause of the injury is known, the patient can be pronounced dead (by neurological criteria), and a death certificate is filled out with the time of death noted as the time the protocol was completed.

## Confirmatory Testing

Many tests can be used to corroborate the brain death examination. Most of these tests measure cortical activity in some way. However, it is possible to meet the criteria for brain death when only the brain stem has died and the cortex is more or less preserved. Therefore, it is possible to meet the clinical criteria for brain death and still show some evidence of brain activity on these tests. These tests are rarely used since they can generate confusing data, delaying the diagnosis while more tests are performed to confirm or deny previous tests.

1. *Electroencephalography*: Isoelectric EEG is a reliable confirmation of brain death when artefacts are reliably ruled out. Total electrical silence is not necessarily required for brain death, so the tracing must be interpreted by an expert. It is important to note that an isoelectric EEG can be obtained after drug intoxication, such as intoxication with barbiturates [16], and some residual electrical activity may persist after brain stem death [17]. For these reasons, EEG is rarely used as a confirmation.
2. *Evoked responses*: [18] Brain stem auditory evoked potentials (BAEPs) and median nerve somatosensory evoked potentials (SSEPs) can be used for diagnosing brain death. BAEPs are signals generated at the level of the auditory nerves and brain stem in response to an acoustic stimulus. SSEPs are waves of neural activity generated from the neural structures along the afferent somatosensory pathways that are generated after electrical stimulation of a peripheral nerve. The pathway starts at a peripheral nerve and then ascends via the brachial plexus, upper cervical cord, dorsal column nuclei, ventro-posterior thalamus and sensory cortex. Bilateral absence of specific waves (N20–P22) following median nerve stimulation is a consistent and confirmatory laboratory finding following brain death.
3. *Angiography*: The absence of blood flow to the brain substance invariably results in the destruction of brain tissue and brain death. Angiography for the determination of brain death is influenced neither by central nervous system depressant drugs nor hypothermia.
4. *Transcranial Doppler sonography*: Transcranial Doppler (TCD) sonography uses a 2-MHz ultrasonic probe affixed to the temporal area, and the flow velocity of each of the major intracranial arteries is measured. In brain death, the cerebral perfusion pressure approaches zero, and TCD demonstrates systolic spikes, undetectable flow (i.e. no signal) or reversal of blood flow in diastole (i.e. to-and-fro or oscillating waveform) [19]. These patterns are highly specific for brain death [20, 21].

## Spinal Reflexes

Although the patient is dead by neurological criteria, there remains the potential for persistent spinal cord viability resulting in spurious jerking reflexes of the extremities [22]. The ‘triple reflex’ (flexion at the hip, knee and ankle) in response to stimulation of the sole of the foot is not uncommon and may persist several hours after brain death. These movements are not indicative of cortical or brain stem function and should not be confused with whole brain viability [23]. If the brain death protocol has been performed rigorously and injury is confirmed on MRI or CAT, the diagnosis should not be in question.

---

## Problems with the Concept of Brain Death

There is a difference between a diagnosis of death and a prognosis of death. In 1981, the President’s Commission broke with the past and established brain death as a diagnosis of death and not simply a tool for predicting the inevitability of death [3]. However, the language used in the Uniform Determination of Death Act (UDDA) opened the door for more expanded and creative definitions of death:

An individual who has sustained either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem, is dead. [24]

This language blurred the concept of whether there are two kinds of death (cardiac or brain), as opposed to a single diagnosis and a contiguous prognosis. This argument persists today and has become quite involved. Ethicists maintain that the criteria used to fulfil the definition of death should be both necessary and sufficient [25]. This is not an easy standard to meet. For example, loss of consciousness is necessary for death, but is not sufficient. Loss of heart beat and breathing is sufficient for death, but is not necessary if brain death is present. Patients with cardioplegia in open heart surgery are not dead and certified dead patients may continue to have cardiac function in intensive care units (ICUs). Only whole brain death meets the necessary as well as sufficient conditions.

In addition, there is a logical problem with the idea of the brain as the fundamental orchestrator of all body functions. It has been pointed out that many organ functions are, for variable periods, not obligately linked to the brain as an integrating controller. Moreover, the current rules do not require that every brain cell be dead for brain death to be declared—only those cells that contribute to the integration of the organism as a whole need be dead [26]. Death occurs when ‘critical’ parts of the brain responsible for integrated functioning of the rest of the body cease functioning. Therefore, the patient does not have to declare diabetes insipidus to be brain dead. We still do not accurately know how much brain death is ‘enough’ and so many of the lines we draw are arbitrary. For example, pregnant patients on life



support have gone on to deliver babies by Caesarean section months after having been declared brain dead.

Another wrinkle in the fabric of brain death occurred in December of 2013. The family of a young woman clinically established as dead by neurologic criteria rejected the medicolegal findings of death and contacted an attorney to argue in court that the patient was not dead and required continued life support [27]. Breaking with usual tradition, a Court Judge ruled that the Hospital must keep the patient on a ventilator for further medical opinions, leading to a series of conflicting arguments (<http://www.renewamerica.com/columns/byrne/131224>; <http://www.cnn.com/2014/01/02/opinion/veatch-defining-death/>). At the time of this writing, the young woman is said to be maintained at a private skilled nursing facility 3 years later but no reliable physician has examined her so it's unclear what her exact condition is.

This situation brings out some important facets involving public acceptance of death by neurologic criteria. Medical experts are unwilling or unable to recommend enforcing the legal definition of death by neurologic criteria. The public, especially the American public is steeped in the tradition of personal autonomy such that if they can decline treatment, they want to be able to demand it through an attorney. The same public has grown increasingly suspicious of the diagnosis of death in a warm, pulsating, ventilating body with all the appearances of viability. Bioethicists and physicians cannot even among themselves come to a consensus that there is only one kind of death and whether the neurologic criterion can certify it.

---

## Death and Identity: The Human Condition

An alternative definition of death is the irreversible loss of the structural information that encodes personal identity and mentation (Darwin, Michael; personal communication). The supposition is that life is not necessarily dependent upon continuous dynamic function. Is a tobacco mosaic virus or T-4 phage dead? Is it less dead if its constituent parts can be shaken in solution and they self-assemble into a viable virus capable of self-replication? Any meaningful definition of death is then suggested by an information-theoretic criterion. In other words, does the patient contain enough undamaged structure (information) to infer his healthy working state from his current non-functional one? Granted, the technology to transform one state to another may not (yet) be available, but this says nothing about what is theoretically possible [27, 28]. According to this definition, the death of an individual person is different from the death of a generic human because of the issue of identity. Like death, identity is a variable continuum, but with binary features in which the difficult and yet unresolved issue of 'how much' and 'what kind' of information loss constitutes destruction of personal identity.

In the analogue version of our current concept of brain death, the difference between tearing up a book and burning it is a clear delineation. In the torn up book, there is no fundamental barrier in physics to recovering its information content.

However, burning the book invokes the laws of thermodynamics to irreversibly destroy the information. Since the very definition of death is irreversibility and the brain is a material system governed by physical law, you have to look to physics for your ultimate definition of irreversibility.

However, in the digital version of identity-defined death, letters sequentially removed from a book alter its readability (identity). Quite a lot of removal is tolerable because it is usually easy to infer what a missing letter should be. However, removal of whole strings of letters, or in some cases even a few critical letters can change the meaning of the book. At some finite point, the book is not readable, or is transformed by attempts to restore it because there are too many possible substitutions and it ceases to be the same book. This is not an academic exercise. It is a very real issue that will become more acute as medicine advances.

Consider a future, hypothetical end-stage dementia patient who has a functionally obliterated cortex and is ‘rescued’ by embryonic stem cells that regenerate a new cortex within the framework of the old one [29, 30]. This person remembers nothing of who he was, even though he had continuous brain stem function and even persistence of consciousness throughout the whole process of illness and ‘recovery’. Is he ‘dead’, going by the criteria of identity? Should he be an organ donor? After repair, is he the same person or a new one? Should we await future technology capable of redefining brain death before we irrevocably act on our current definitions?

---

## Withdrawing Care

Once a patient is declared dead by whatever criteria, the family is told that the patient is dead and artificial life support will be removed. Surrogates cannot refuse to accept brain death as a criterion for death and demand continuance of life support, unless the patient resides in a state that allows such a refusal on religious grounds [30, 31]. The decision to withdraw artificial life support from a brain-dead patient is made before any mention of organ donation (organ donation is a completely separate issue). As brain death confirmed by protocol is synonymous with death, a death certificate is filled out, noting the time of death as the time the protocol was completed. The withdrawal process is simply the removal of the machines. The patient is considered already dead and there is no ‘dying process’ to palliate.

---

## Implications for Future Definitions of Death

The idea that brain death is equivalent to death is now internationally established and codified. A recent evidence-based guideline update of the American Academy of Neurology for determining brain death in adults raises questions that we have grappled with for many years [28, 31]. Debates continue over how much brain function must be irreversibly injured for a diagnosis of brain death to be made and

whether there is more than one kind of death. That said, there are disturbing differences between a corpse in a morgue and a brain-dead patient. If the brain-dead patient is a corpse, he or she is certainly a corpse with some unusual properties—one that breathes, circulates blood, digests food, filters wastes and is capable of carrying a pregnancy to term [29, 32]. These considerations show that the precise moment when death occurs cannot be accurately pinpointed, and raise the issue of whether there is a practical or ethical difference between being dead, being almost dead and being in the process of dying. It is clear that a brain-dead patient can be maintained on life-sustaining treatment for much longer than was once thought and still retain definite characteristics of a living being. The organism as a whole, though disabled, is not yet dead and should not be represented as such—a fact that may have important consequences for our future conceptions of death and of life in death.

---

## References

1. Crippen D. Medical treatment for the terminally ill: the 'risk of unacceptable badness. *Crit Care*. 2005;9:317–8.
2. Bernat JL, Culver CM, Gert B. On the definition and criteria of death. *Ann Intern Med*. 1981;94:389–94.
3. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the study of ethical problems in medicine and biomedical and behavioral research. *JAMA*. 1981;246:2184–6.
4. Crippen DW, Whetstone LM. Ethics review: dark angels—the problem of death in intensive care. *Crit Care*. 2007;11:202.
5. Wertheimer P, Jouve M, Descotes J. À propos du diagnostic de la mort du système nerveux dans les comas avec arrêt respiratoire traités par respiration artificielle. *Presse Med*. 1959;67:87–8.
6. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968;205:337–40.
7. Bernat JL. A defense of the whole-brain concept of death. *Hast Cent Rep*. 1998;28:14–23.
8. Izac SM. Quality assurance in determinations of brain death. *Am J Electroneurodiagnostic Technol*. 2004;44:159.
9. Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1995;45:1012–4.
10. Whetstone L. Bench-to-bedside review: when is dead really dead—on the legitimacy of using neurologic criteria to determine death. *Crit Care*. 2007;11:208.
11. Uniform determination of death act. 12 Uniform laws annotated. 320 (1990 Supp). [http://www.lchc.ucsd.edu/cogn\\_150/Readings/death\\_act.pdf](http://www.lchc.ucsd.edu/cogn_150/Readings/death_act.pdf).
12. Hammer MD, Crippen D. Brain death and withdrawal of support. *Surg Clin North Am*. 2006;86:1541–51.
13. Morenski JD, Oro JJ, Tobias JD, et al. Determination of death by neurological criteria. *J Intensive Care Med*. 2003;18:211.
14. Whetstone L, Streat S, Darwin M, et al. Pro/con ethics debate: when is dead really dead? *Crit Care*. 2005;9:538–42.
15. Safar P, Bircher N. Cardiopulmonary cerebral resuscitation. 3rd ed. Philadelphia: WB Saunders; 1988.
16. Segura T, Jimenez P, Jerez P, et al. Prolonged clinical pattern of brain death in patients under barbiturate sedation. *Neurologia*. 2002;17:219.

17. Grigg MM, Kelly MA, Celesia GG, et al. Electroencephalographic activity after brain death. *Arch Neurol*. 1987;44:948.
18. Wang JT, Young GB, Connolly JF. Prognostic value of evoked responses and event-related brain potentials in coma. *Can J Neurol Sci*. 2004;31:438–50.
19. Hassler W, Steinmetz H, Gawlowski J. Transcranial Doppler ultrasonography in raised intracranial pressure and intracranial circulatory arrest. *J Neurosurg*. 1988;68:745.
20. Feri M, Ralli L, Felici M, et al. Transcranial Doppler and brain death diagnosis. *Crit Care Med*. 1994;22:1120.
21. Petty GW, Mohr JP, Pedley TR, et al. The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology*. 1990;40:300–3.
22. Saposnik G, Basile VS, Young GB. Movements in brain death: a systematic review. *Can J Neurol Sci*. 2009;36:154–60.
23. Jain S, DeGeorgia M. Brain death-associated reflexes and automatisms. *Neurocrit Care*. 2005;3:122–6.
24. Crippen D. Donation after cardiac death: perceptions versus reality. *J Intensive Care Med*. 2008;23:347–8.
25. Whetstone L. On the definition and criteria of death: when is dead dead and why some donation after cardiac death donors are not [PhD Dissertation]. Duquesne University, Department of Health Care Ethics; 2006.
26. Bernat JL. The biophilosophical basis of whole-brain death. *Soc Philos Public Policy*. 2002;19:337.
27. Crippen D. Changing interpretations of death by neurologic criteria: the McMath case. *J Crit Care*. 2014;29:870–1.
28. Darwin MG, Leaf JD, Hixon H. Neuropreservation of Alcor patient A-106 (from Cryonics, February and March, 1986).
29. Wowk B, Darwin M. ‘Realistic’ scenario for nanotechnological repair of the frozen human brain. Reprinted from cryonics: reaching for tomorrow. Scottsdale: Alcor Life Extension Foundation; 1991.
30. Olick RS. Brain death, religious freedom, and public policy: New Jersey’s landmark legislative initiative. *Kennedy Inst Ethics J*. 1991;1:275.
31. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM, American Academy of Neurology. Evidence-based guideline update: determining brain death in adults. Report of the quality standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74:1911–8.
32. Powner DJ, Bernstein IM. Extended somatic support for pregnant women after brain death. *Crit Care Med*. 2003;31:1241.